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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

Whereto Tuberculosis? The First Seven Years of the Antimicrobial Era, 1947–1953. Godias J. Drolet and Anthony M. Lowell 419
Pulmonary Function Before and After Resection of Tuberculous Lung Segments. Warren J. Taylor, John B. Petter, and James L. Whittenberger 453
Pulmonary Nitrogen Clearance as a Criterion of Ventilatory Efficiency. Ulrich C. Lupt, Elizabeth H. Roorbach, and Rodger E. MacQuigg 465
Intermittent Positive Pressure Breathing in Patients with Pulmonary Tuberculosis. Joseph F. Tomashefski and Peter A. Tchen 479
Mortality and Relapse of Uncomplicated Advanced Pulmonary Tuberculosis Before Chemotherapy: 1,504 Consecutive Admissions Followed for Fifteen to Twenty-Five Years. I. The Relationship of Factors Determined on Admission. Roger S. Mitchell 487
Mortality and Relapse of Uncomplicated Advanced Pulmonary Tuberculosis Before Chemotherapy: 1,504 Consecutive Admissions Followed for Fifteen to Twenty-Five Years. II. The Relationship of Type of Treatment and Status on Discharge. Roger S. Mitchell ... 502
On the Prognosis of Childhood Tuberculosis. An Eighteen-Year Follow-Up Report. Nils Levin . 513

Case Reports:
Transitory Exacerbation of Fever and Roentgenographic Findings During Treatment of Tuberculosis in Children. C. B. Choremis, C. Padiatellis, D. Zoumboulakis, and D. Yannakos 527
A Case of Air Embolus During Pneumoperitoneum. Vicente López Majano 537

Notes:
Resistance of Guinea Pigs to Infection with Small Numbers of Virulent Tubercle Bacilli Mixed with BCG. Diran Yegian and Vera Budd 539
Blood Concentration Studies with Buffered Para-Aminosalicylic Acid Tablets. Edward N. Deeb and Guy R. Vitagliano 543
Para-Aminosalicylic Acid-Resin Complex. Studies in Absorption, Serum Electrolytes, and Tolerance. A. Gerson Hollander 548
Correspondence: The Fate of the Irregular Discharge Tuberculosis Patient. Stanton T. Allison 552
Books 555
American Trudeau Society:
The Award of the Trudeau Medal for 1954 559
Abstracts 119

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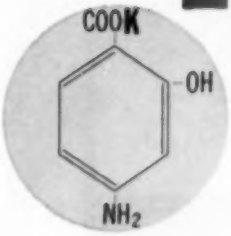

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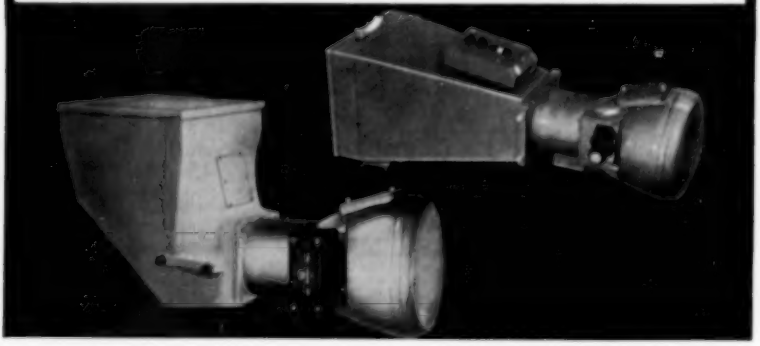

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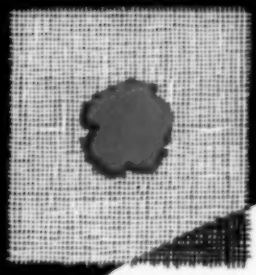

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Clinical sequelae of protein malnutrition include kwashiorkor and liver disease.[1] In kwashiorkor the caloric intake may approximate normal, but the dietary protein is less than the necessary minimum in quality and quantity. Many tropical diets supply 10 to 15 per cent of the calories in the form of vegetable protein. Kwashiorkor may follow infections, especially of the gastrointestinal tract. Diets below 10 per cent in protein calories lead to frank protein malnutrition, including signs and symptoms of kwashiorkor.

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2. Davies, J.N.P.: Kwashiorkor, Trans. Ninth Conf. on Liver Injury, Josiah Macy, Jr. Foundation, 1950, p. 109.
3. The National Food Situation, Washington, D. C., Agricultural Marketing Service, United States Department of Agriculture, Oct. 29, 1954, p. 4.

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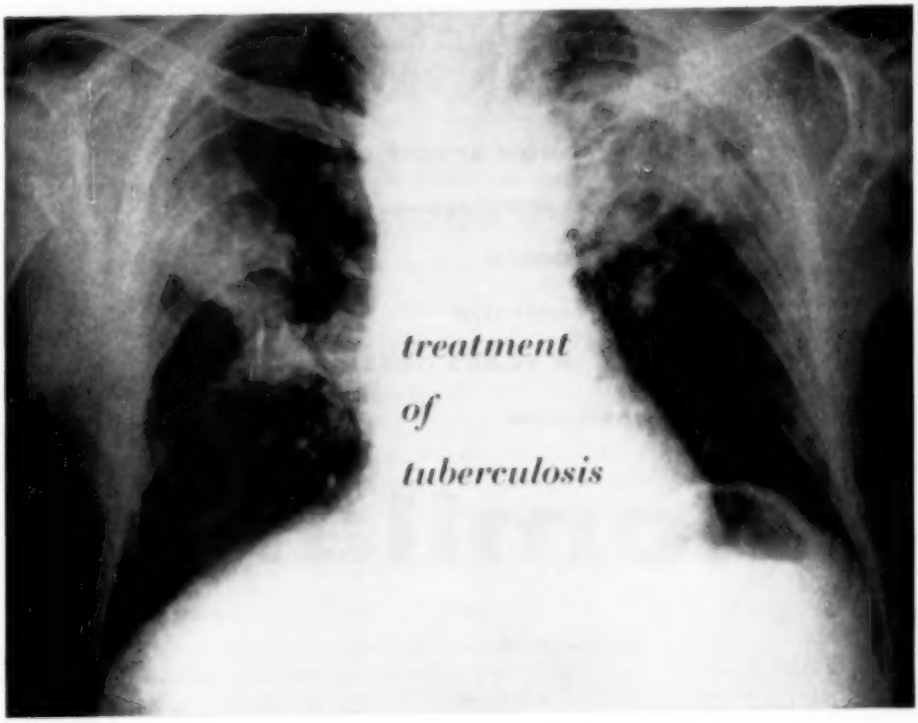

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 72 | *October, 1955* | NUMBER 4

WHERETO TUBERCULOSIS? [1, 2]

The First Seven Years of the Antimicrobial Era, 1947–1953

GODIAS J. DROLET AND ANTHONY M. LOWELL

(Received for publication June 6, 1955)

TUBERCULOSIS MORTALITY AND MORBIDITY

Never since urbanization, privation, and hardships made mankind susceptible to invasion by the tubercle bacillus have its deathly inroads been brought so speedily under control as in recent years. Its captaincy of the "men of death" in New York City, the largest center of population in America, ended only with the close of the nineteenth century. In 1954, in the same, much larger community, tuberculosis as a leading cause of death was relegated to tenth place.

TUBERCULOSIS AT THE BEGINNING OF THE CENTURY

With the tuberculosis death rate in 1954 in the United States down to 10 per 100,000 population, it is difficult to realize the extreme mortality rates which prevailed not so long ago. In 1912, an investigation by Neill and Perry (1) on the condition of women and child wage-earners in the United States, made at the request of the United States Senate, brought out that, among operatives in the cotton mills of Fall River, Manchester, and Pawtucket, during 1905, 1906, and 1907, tuberculosis "showed an extraordinary excess," the tuberculosis death rate averaging annually 320 per 100,000. Among girls aged fifteen to twenty, the death rate was 219 per 100,000. Among young women twenty to twenty-five years old, the rate was 304. Among those twenty-five to thirty, it was 443; and, in the age group thirty to thirty-five, it reached the unenviable peak of 473.

In terms of today, these death rates from tuberculosis, for instance, among workers under twenty in the New England cotton mills, when compared with the rates prevailing in the United States in 1951 in the same age group of females, were thirty-four times that prevailing recently, which was only 6.5 per 100,000 population. Among women twenty-five to thirty-five, the death rate of the operatives in Fall River, Manchester, and Pawtucket was between twenty-five and twenty-eight times as great as rates nowadays in the same age groups.

So rapid have been the changes in the prevalence of tuberculosis and in its

[1] From the New York Tuberculosis and Health Association, New York, New York.

[2] Presented at the 32nd annual meeting of the American Epidemiological Society, University of Minnesota, April 2, 1955.

mortality during the past few years, especially since 1947, that it has become important to establish "bench marks" and to record carefully what has been happening.

ANTIMICROBIAL THERAPY

Improvement in the treatment of tuberculosis through the development of antimicrobial drugs and more successful thoracic surgery has been the basic event in the recent history of the disease. Let us first recall that, while streptomycin was discovered in 1944 and subjected to careful clinical study in 1945 and 1946, it was primarily in 1947 that this life-saving drug became generally available. Second, it was in 1949 that para-aminosalicylic acid (PAS), developed abroad, likewise came into hand here. The latter, while not too effective alone, in combination with streptomycin contributes advantageously by delaying the emergence of resistant strains of tubercle bacilli and thereby lengthening the therapeutic effect of the drugs. Third, it was in 1952 that the general use of isoniazid became possible. This drug was employed dramatically, it will be recalled, originally in late 1951 in New York City at the Sea View Hospital and, likewise, independently, at the New York Hospital-Cornell Medical Center. One may, therefore, speak of the period from 1947 to 1953 as the first seven years of the chemotherapeutic era in the treatment of the most serious infectious disease affecting mankind for centuries. And, the great successes of surgery in tuberculosis during those same recent years have been generally ascribed to the new effective drugs, improved anesthesia, and improved surgical techniques. Prior to 1947, the treatment of tuberculosis had been largely dependent on bed rest and collapse therapy and, as noted by Drolet (2), the case fatality rates had shown but little improvement for more than twenty years.

TUBERCULOSIS MORBIDITY AND MORTALITY IN THE FIRST SEVEN YEARS (1947–1953) OF THE ANTIMICROBIAL ERA

Thanks to the courtesy of a number of official authorities of various countries, it is possible at the moment to set down nation-wide records with regard to both the mortality from tuberculosis and, to a certain extent its morbidity, which permit an unusual appraisal of recent conditions. The seven years, from 1947 to 1953 inclusive, have therefore been selected for recording and testing the progress made and the effect, particularly, of the new antimicrobials in various parts of the world where detailed annual registration is available.

Tuberculosis Mortality

In table 1 are shown the tuberculosis death rates annually in thirty different countries and the Commonwealth of Puerto Rico during the seven years mentioned and the change in mortality between the first and last years, namely 1953 as compared with 1947. At the same time, as a background to appraise the progress made, the death rates in 1940 as against 1930 and the extent of the change which occurred during that decade are presented.

In twenty-three of these thirty different countries and the one commonwealth, the decline in the tuberculosis mortality between 1947 and 1953 has

TABLE 1

TUBERCULOSIS DEATH RATES* IN THIRTY COUNTRIES AND THE COMMONWEALTH OF PUERTO RICO WITH CHANGES BETWEEN 1930 AND 1940, AND BETWEEN 1947 AND 1953

Country	1930	1940	Change 1940/30	1947	1948	1949	1950	1951	1952	1953	Change 1953/47
			per cent								*per cent*
United States	71	46	−35	33	30	26	22	20	16	12	−64
Puerto Rico	263	260	−1	192	176	146	130	119	93	47	−76
Canada	77	50	−35	42	36	32	26	24	17	12	−71
Mexico	69	57	−17	50	47	44	41	42	37	31	−38
Uruguay	139	109	−22	99	89	70	62	53	46	40	−60
Argentina	129	91	−22	72	57	52	48	44	42	40	−44
Chile	264	261	−1	225	226	201	158	148	114	82	−64
England-Wales	87	67	−23	55	51	45	36	32	24	20	−64
Scotland	88	81	−8	80	75	68	54	43	32	26	−68
Northern Ireland	129	98	−24	73	69	59	48	45	30	23	−68
Eire	130	125	−4	125	104	89	78	73	54	40	−68
Iceland	216	86	−60	53	34	26	20	21	14	9	−83
Finland	254	212	−17	168	157	132	94	84	58	45	−73
Sweden	126	71	−44	52	42	28	22	22	18	15	−71
Norway	149	81	−46	56	51	38	29	24	20	16	−71
Denmark	71	35	−51	30	25	19	14	13	11	10	−67
Netherlands	75	44	−41	37	28	25	19	16	12	9	−76
Belgium	92	68	−26	63	55	49	43	38	27	28	−56
Luxemburg	84	63	−25	65	58	47	44	29	24	17	−74
Switzerland	125	78	−38	68	53	42	35	35	25	23	−66
Germany§	79	74‡	−6	73	67	49	39	37	27	21	−71
Austria	139	102	−27	93	88	72	55	53	46	34	−63
France	158	140	−11	79	74	67	58	61	44	37	−53
Italy	112	74	−34	77	61	49	40	43	28	23	−70
Spain	123	113	−8	125	115	116	105	93	56	40	−68
Portugal	192	153	−20	155	150	152	144	133	97	63	−59
Union, S. Africa	47	35	−26	31	30	26	24	20	15	—	−52†
Ceylon	68	62	−9	56	57	57	53	50	38	30	−46
Australia	50	37	−26	30	28	25	20	18	15	11	−63
New Zealand	46	39	−15	31	27	25	23	21	15	12	−61
Japan	187	210	+12	188	179	168	146	111	82	66	−65

* Per 100,000 population.

† Change from 1947 to 1952 only.

‡ Year 1939.

§ Period 1947–1953, Federal Republic.

exceeded 60 per cent. It has been well said that, since the discovery and use of streptomycin, PAS, and isoniazid only a few years ago, these drugs have already given life to hundreds of thousands of those sick from tuberculosis throughout the world.

With regard to the United States alone, it may be noted that the tuberculosis death rate between 1930 and 1940 was declining, on an average, by 3.5 per cent annually. But, between 1947 and 1953, in seven years only, the death rate fell from 33 per 100,000 to 12, or 64 per cent—an average of 9 per cent annually.

During the decade 1930 to 1940, of the thirty countries and one commonwealth listed in table 1, in every country but Japan the tuberculosis death rate was dropping. However, in no country did the decline begin to compare with that which occurred during the seven years from 1947 to 1953. Except for Mexico, Argentina, France, Portugal, and Ceylon, the reduction in the tuberculosis death rate has ranged all the way from 60 per cent in Uruguay to 83 per cent in Iceland during the more recent period; and, even in the five countries mentioned as exceptions, the decline in the death rate has amounted to between 38 and 59 per cent.

In order to visualize the tuberculosis death rates prevailing previously and lately, they have been plotted in figure 1 annually since 1930 for each of the thirty countries and one commonwealth mentioned. The steepness of the decline after 1945 and its acceleration more recently are obvious. A line drawn at the beginning of the year 1947 would virtually mark the division between two periods with different forms of treatment in tuberculosis and the consequent results. In one period, that prior to 1947, bed rest and collapse therapy—mainly artificial pneumothorax—represented the general therapeutic practice. In the other period which began in 1947, the antimicrobial era, the therapeutic practice was characterized by chemotherapy and excisional surgery in hospital treatment, followed increasingly of late by the so-called "ambulatory treatment," or "home care" programs.

Tuberculosis Morbidity

Mortality records are only one index of the prevalence of tuberculosis—a "tail-end" one. Morbidity reporting is the second index, the main basis at the present time for a tuberculosis control program. Finally, a third index is the prevalence of infection as revealed by the tuberculin test.

Morbidity reports are not so readily available as mortality returns. Nevertheless, registration of cases, although limited in extent and dependability, is still, within certain limits and understanding, far better than no information at all. While reporting practices undoubtedly vary in different areas and countries, still, within the same locality the trend of reporting, especially of new cases, is significant. Moreover, over a short period of time only, cases are likely to have been reported along customary and comparable lines.

In tables 2, 3, 4, 5, and 6, there has been assembled the annual registration of new cases of tuberculosis for the seven years from 1947 to 1953 in fifteen different countries and one commonwealth: the United States of America, Canada, France, West Germany, England and Wales, Scotland, Northern Ireland, Eire, Norway, Sweden, Denmark, Finland, Iceland, New Zealand, Puerto Rico,[3] and Australia. Additional data are also presented, either for contrast because of

[3] A commonwealth.

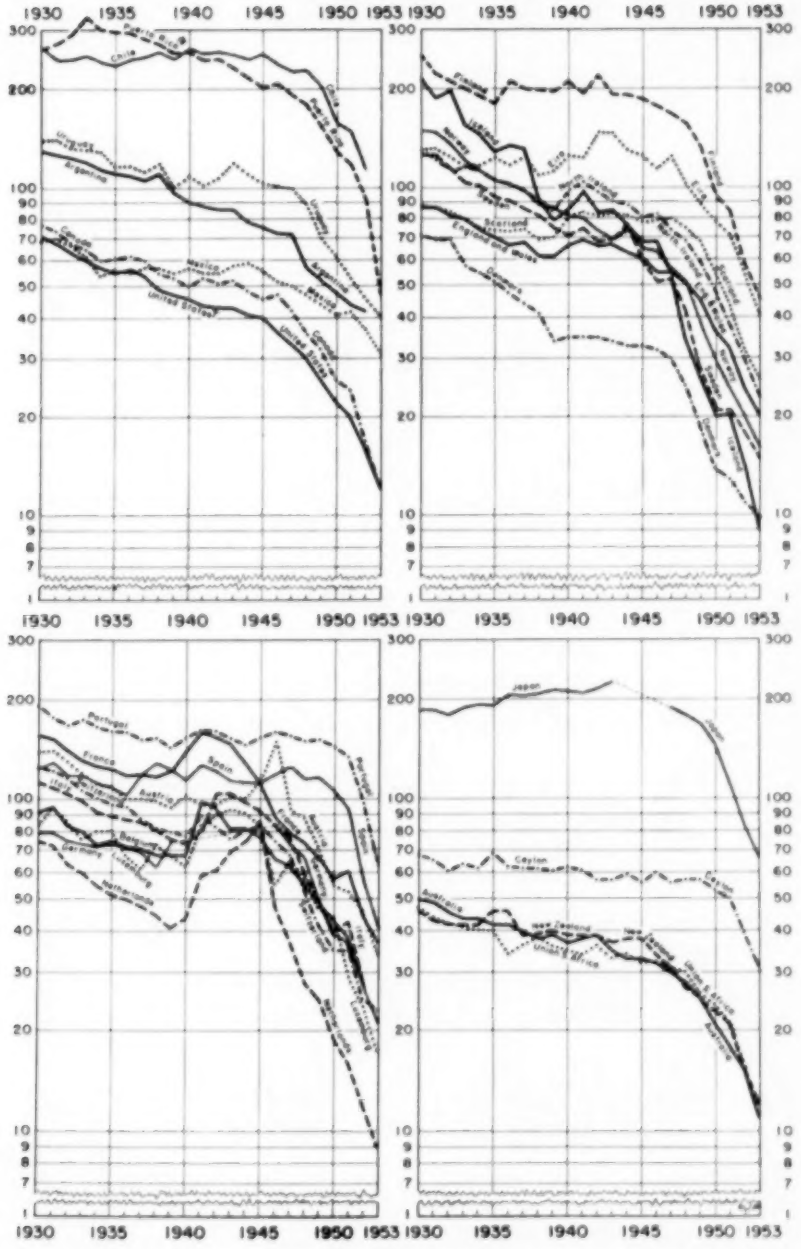

FIG. 1. Tuberculosis death rate (per 100,000 population) in various countries and the commonwealth of Puerto Rico between 1930 and 1953.

* Commonwealth.

† Exclusive of Puerto Rico.

TABLE 2

TUBERCULOSIS MORBIDITY AND MORTALITY, PRIMARILY BETWEEN 1947 AND 1953, IN THE UNITED STATES, CANADA, FRANCE AND GERMANY

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†	Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent						*per cent*		
	United States						Canada				
1930	124,940	88,010	70	102	71	1930	6,562§	8,075	—	—	77
1940	102,984	60,428	59	78	46	1940	10,226	5,789	57	88	50
1947	134,946	48,064	36	94	33	1947	13,739	5,449	40	107	42
1948	137,006	43,833	32	93	30	1948	12,363	4,773	39	94	36
1949	134,865	39,100	29	90	26	1949***	12,777	4,295	34	95	32
1950	121,742	33,959	28	80	22	1950	12,429	3,583	29	91	26
1951	118,491	30,863	26	77	20	1951	11,152	3,417	31	80	24
1952	109,837	24,261	22	70	16	1952	10,506	2,457	23	73	17
1953	106,925	19,393‡	18	67	12	1953	10,572	1,810	17	72	12
Change 1953/47	−28,021 =21%	−28,671 =60%	−18	−27 =29%	−21 =64%	Change 1953/47	−3,169 =23%	−3,639 =67%	−23	−35 =33%	−30 =71%
	France						Germany				
1930	¶	65,803	—	—	158	1930‖	—	50,646	—	—	79
1940	—	53,320	—	—	140	1939‖	—	51,195	—	—	74
1947	67,877	31,707	47	167	79	1947	—	30,302	—	—	73
1948	68,328	30,637	45	166	74	1948	185,622	31,066	17	400	67
1949	63,244	27,953	44	152	67	1949	147,001	23,324	16	312	49
1950	62,107	24,282	39	149	58	1950	122,928	18,806	15	258	39
1951	62,984	25,703	41	149	61	1951	117,546	17,849	15	243	37
1952	60,100	18,634	31	142	44	1952	110,797	13,281	12	227	27
1953	60,074	15,687	26	140	37	1953	107,538††	10,433	10	219	21
Change 1953/47	−7,803 =11%	−16,020 =51%	−21	−27 =16%	−42 =53%	Change 1953/47	−78,084 =42%**	−19,869 =66%	−7	−181 =45%	−52 =71%

* All forms.
† Per 100,000 population.
‡ Provisional.
§ Registration incomplete.
*** 1950 and thereafter includes Newfoundland.
¶ New cases registered at dispensaries.
‖ Eastern and Western Germany.
** 1953/1948.
†† Includes 30,281 "open cases," 65,195 "acktiv geschlossen," and 15,321 of "other forms."
Population estimated as of 1953: United States, 159,629,000 (including Armed Forces overseas); Canada, 14,756,000; France, 42,742,000; German Republic, 48,994,000.

TABLE 3

TUBERCULOSIS MORBIDITY AND MORTALITY, PRIMARILY BETWEEN 1947 AND 1953, IN THE UNITED KINGDOM AND EIRE

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†	Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent						*per cent*		
	England–Wales						Scotland				
1930	70,110	34,816	50	176	87	1930	9,913	4,286	43	203	88
1940	49,967	28,144	56	119	67	1940	7,722	3,979	52	157	81
1947	55,407	23,551	43	129	55	1947	10,117	4,095	40	197	80
1948	56,127	21,993	39	129	51	1948	10,046	3,901	39	194	75
1949	55,323	19,908	36	126	45	1949	10,300	3,484	34	199	68
1950	52,062	15,969	31	119	36	1950	9,681	2,775	29	187	54
1951	52,046	13,806	27	119	32	1951	9,200	2,179	24	180	43
1952	50,332	10,585	21	115	24	1952	8,688	1,612	19	170	32
1953	48,832	8,902	18	111	20	1953	8,844	1,341	15	173	26
Change 1953/47	−6,575 =12%	−14,649 =62%	−25	−18 =14%	−35 =64%	Change 1953/47	−1,273 =13%	−2,754 =67%	−25	−24 =12%	−54 =68%
	Northern Ireland						Eire				
1930	—	1,591	—	—	129	1930	—	3,825	—	—	131
1940	599‡	1,266	—	—	98	1940	4,772	3,685	77	161	125
1947	1,517‡	974	—	113‡	73	1947	5,942	3,700	62	200	124
1948	2,862	932	33	212	69	1948	6,073	3,103	51	203	104
1949	2,575	798	31	189	59	1949	7,552	2,712	36	253	91
1950	2,153	661	31	157	48	1950	6,796	2,380	35	229	80
1951	2,043	617	30	149	45	1951	6,685	2,107	32	226	71
1952	1,819	410	23	132	30	1952	6,795	1,579	23	230	54
1953	1,661	316	19	120	23	1953	6,602	1,190	18	224	40
Change 1953/48	−1,201 =42%	−658§ =68%	−14	−92 =43%	−50§ =68%	Change 1953/47	+660 =11%	−2,510 =58%	−44	+24 =12%	−84 =68%

* All forms.
† Per 100,000 population.
‡ Prior to September 1, 1947, "acute infectious cases" only; thereafter, all forms.
§ 1953/1947.
Population, estimated as of 1953: England and Wales, 44,000,000; Scotland, 5,117,600; Northern Ireland, 1,384,000; Eire, 2,945,000.

TABLE 4

TUBERCULOSIS MORBIDITY AND MORTALITY, PRIMARILY BETWEEN 1947 AND 1953, IN NORWAY, SWEDEN, DENMARK, AND FINLAND

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent		
		Norway			
1930	—	4,197	—	—	150
1940	3,877	2,415	62	130	81
1947	3,719	1,760	47	118	56
1948	3,441	1,641	48	108	51
1949	3,505	1,242	35	108	38
1950	3,135	947	30	96	29
1951	2,989	783	26	91	24
1952	2,551	667	26	77	20
1953	3,073	539	18	91	16
Change 1953/47	−646 =17%	−1,221 =69%	−29	−27 =23%	−40 =71%
		Denmark (Pulmonary Tuberculosis)			
1930	3,889	1,899	49	110	54
1940	2,687	1,121	42	70	29
1947	3,522	1,010	29	85	24
1948	3,351	895	27	80	21
1949	2,906	672	23	69	16
1950	2,514	505	20	59	12
1951	2,412	508	21	56	12
1952	2,060	423	21	48	10
1953	1,764	341	19	40	8
Change 1953/47	−1,758 =50%	−669 =66%	−10	−45 =53%	−16 =67%

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent		
		Sweden			
1930	—	7,715	—	—	126
1940	18,421	4,484	24	290	71
1947	13,708	3,516	26	202	52
1948	12,808	2,858	22	186	42
1949	11,611	1,961	17	169	28
1950	10,550	1,525	14	150	22
1951	10,108	1,561	15	143	22
1952	8,516	1,293	15	120	18
1953	7,724	1,044	14	108	15
¶ Change 1953/47	−5,984 =44%	−2,472 =70%	−12	−94 =47%	−37 =71%
		Finland			
1930	—	8,771	—	—	254
1940	5,189¶	7,842	—	140	212
1947	9,245	6,493	70	240	168
1948	7,341	6,154	84	188	157
1949	7,128	5,218	73	180	132
1950	5,935	3,754	63	148	94
1951	11,144	3,390	30	275	84
1952	11,710	2,359	20	286	58
1953	11,426	1,848	16	276	45
Change 1953/47	‡	−4,645 =72%	−14§	+1§ =0.4%	−123 =73%

* All forms.
† Per 100,000 population.
‡ Reorganization in 1951 brought entire population in unified program; previously it was incomplete.
§ 1953/1951.
¶ Registration incomplete.
Population, estimated as of 1953: Norway, 3,359,000; Sweden, 7,171,461; Denmark, 4,369,200; Finland, 4,141,000.

TABLE 5

TUBERCULOSIS MORBIDITY AND MORTALITY, PRIMARILY BETWEEN 1947 AND 1953, IN ICELAND, NEW ZEALAND, PUERTO RICO, AND AUSTRALIA

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†	Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent						*per cent*		
		Iceland						New Zealand			
1930	462	232	50	430	216	1930	1,244‡	649	—	—	46
1940	435	104	24	360	86	1940	1,186	600	51	77	39
1947	369	71	19	275	53	1947	1,692	524	31	109	31
1948	280	47	17	204	34	1948	1,619	469	29	94	27
1949	259	36	14	185	26	1949	1,472	435	30	84	25
1950	234	29	12	164	20	1950	1,547	412	27	86	23
1951	250	31	12	172	21	1951	1,375	383	28	75	21
1952	209	20	10	141	14	1952	1,482	273	18	79	15
1953		14			9	1953	1,439	238	17	75	12
Change 1953/47	−160§ =43%	−57 =80%	−9§	−134§ =49%	−44 =83%	Change 1953/47	−253 =15%	−286 =55%	−14	−25 =25%	−19 =61%
		Puerto Rico						Australia			
1930	6,629	4,080	62	428	263	1930	4,768	3,258	68	74	50
1940	9,140	4,886	53	487	260	1940	4,157	2,581	62	59	37
1947	6,367	4,169	65	294	192	1947	3,971	2,261	57	52	30
1948	7,155	3,858	54	327	176	1948	3,707	2,169	59	48	28
1949	7,101	3,205	45	323	146	1949	3,714	1,964	53	47	25
1950	5,688	2,861	50	258	130	1950	4,491	1,675	37	55	20
1951	5,955	2,654	45	267	119	1951	4,635	1,538	33	55	18
1952	6,120	2,092	34	273	93	1952	4,786	1,290	27	55	15
1953	5,246	1,046	20	235	47	1953	4,979	974	20	56	11
Change 1953/47	−1,121 =18%	−3,114 =75%	−45	−59 =20%	−145 =76%	Change 1953/47	+1,008 =25%	−1,287 =57%	−37	+4 =8%	−19 =63%

* All forms.
† Per 100,000 population.
‡ Pulmonary cases only. New Zealand data for European population.
§ 1952/1947.
Population, estimated as of 1953: Iceland, 150,539; New Zealand, 1,924,680; Puerto Rico, 2,229,000; Australia, 8,817,901.

TABLE 6

TUBERCULOSIS MORBIDITY AND MORTALITY, PRIMARILY BETWEEN 1947 AND 1953, IN THE STATES OF NEW YORK AND KANSAS AND THE PROVINCES OF ONTARIO AND QUEBEC

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent		
	State of New York (U.S.A.)				
1930	20,410	8,967	44	164	71
1940	14,065	6,259	44	105	47
1947	12,915	5,363	42	92	38
1948	13,717	5,159	38	95	36
1949	13,911	4,389	32	93	29
1950	12,493	3,811	31	84	26
1951	12,129	3,510	29	81	24
1952	11,661	2,665	23	77	18
1953	11,375	2,004	18	75	13
Change 1953/47	−1,540 =12%	−3,359 =63%	−24	−17 =18%	−25 =66%
	Province of Ontario (Canada)				
1930	—	1,791	—	—	53
1940	2,580	1,011	39	69	27
1947	1,454	1,042	72	35	25
1948	1,576	825	52	37	19
1949	1,434	686	48	33	16
1950	1,431	585	41	32	13
1951	1,291	579	45	28	13
1952	1,287	398	31	27	8
1953	1,412	311	22	29	6
Change 1953/47	−42 =3%	−731 =70%	−50	−6 =7%	−19 =76%

Year	New Cases	Tuberculosis Deaths*	Case Fatality	Case Rate†	Death Rate†
			per cent		
	State of Kansas (U.S.A.)				
1930	1,387	693	58	74	37
1940	757	448	59	42	25
1947	950	321	34	51	17
1948	1,160	242	21	61	13
1949	722	209	29	38	11
1950	552	192	35	29	10
1951	562	192	34	29	10
1952	470	146	31	24	7
1953	386	99	26	19	5
Change 1953/47	−564 =59%	−222 =69%	−8	−32 =63%	−12 =71%
	Province of Quebec (Canada)				
1930	2,251	3,350	—	—	119
1940	3,196	2,503	78	97	76
1947	5,407	2,436	45	146	66
1948	4,899	2,216	45	129	59
1949	5,355	1,898	35	138	49
1950	4,897	1,564	32	123	39
1951	4,203	1,553	37	104	38
1952	4,187	1,108	26	100	27
1953	4,094	844	21	96	20
Change 1953/47	−1,313 =24%	−1,592 =65%	−24	−50 =34%	−46 =70%

* All forms.

† Per 100,000 population, as of 1953: New York State, 15,513,768; State of Kansas, 2,006,000; Province of Ontario, 4,897,000; Province of Quebec, 4,269,000.

largely different racial groups (Ontario and Quebec, Canada); or because of different occupational development groups in the United States (the states of New York and Kansas).

The data presented in these tables indicate what has been frequently noted lately, especially by Edwards and Drolet (3), that, while mortality has been declining rapidly, primarily because of the newer forms of treatment, the incidence, or the number of new cases, is not coming down at the same rate. Specific preventive measures and improvement of socio-economic measures are still lagging behind. To prevention of disease must be added prevention of relapse. Consequently, it is a serious mistake to conclude that, while mortality is rapidly declining, it is not necessary to continue utilizing every known method of control. In fact, there is need for their improvement and greater attention rather than less if satisfactory tuberculosis control is to be achieved.

United States, Canada, France, and West Germany

In the United States, between 1947 and 1953, the annual number of deaths from tuberculosis has fallen from 48,064 to 19,393, or 60 per cent. However, during that period, new cases of tuberculosis have continued to number more than 100,000 annually. In 1947, there were 134,946 new cases reported and, in 1953, 106,925, a decrease in number of 28,021 (21 per cent). In 1940, the ratio of the number of deaths from tuberculosis to the number of new cases reported, which may well be called the *community case fatality*, was still as high as 59 per cent. During the period from 1947 to 1953, the ratio was reduced from 36 to 18 per cent; in other words, cut in half. In relation to the population, the reporting of new cases of tuberculosis, starting at 94 per 100,000 in 1947, was 67 in 1953, a reduction of 29 per cent. For the same years, the death rate came down from 33 per 100,000 to 12, being therefore reduced by two-thirds.

As has been well noted, the number of new cases reported during a particular year represents only a part of the prevalence of tuberculosis in the community. Experience has shown that the total number of cases, old and new, during a particular period is between three and four times the new cases during the same period. In other words, in the United States during 1953 alone, the number of active cases of tuberculosis reached a value between 350,000 and 400,000.

In nearby Canada, where in 1947 the new cases of tuberculosis registered numbered 13,739, the decline to 10,572 in 1953 represented a reduction of 23 per cent. At the same time, the deaths from tuberculosis, which were at first 5,449, numbered only 1,810 in 1953, a drop of 67 per cent in the seven-year period. And in relation to population increase, the case rate per 100,000 population fell by 34 per cent while the death rate came down more than twice as fast, namely, by 71 per cent. The death rate in Canada, from a value of 42 deaths per 100,000 population in 1947, was down to 12 in 1953, the same level which had been attained in the United States. The rapid progress against tuberculosis mortality in Canada lately is all the more impressive when considered against the background of the intensive development going on in industry there, especially in mining, as well as the growth of the population in its cities and newer

communities and the serious remaining health problems faced by its Indian Health Services.

France, ravaged during both World War I and World War II, still pays a heavy toll to tuberculosis. Its death rate in 1940, for instance, was 140 per 100,000, or more than three times that of the United States. However, in recent years, there has been a marked improvement in health conditions in France. Although 60,074 new cases of tuberculosis were still reported in 1953 (table 2), the total was nearly eight thousand (11 per cent) lower than in 1947. During the same period the number of deaths has been cut in half, namely, from 31,707 to 15,687; and, in relation to the population, the death rate was reduced by 53 per cent (from 79 to 37 per 100,000).

No attempt is made here to compare the tuberculosis case or morbidity rates in the different countries under study. It is well realized that the reporting of cases is not done with the same degree of completeness or accuracy in each place. However, there is no doubt that for a particular country the practice is fairly consistent over the years, and the annual records within the same country, especially for a relatively short period, may well be compared. The trend shown is doubtless typical of what is happening there.

Thanks to the late Professor F. Ickert, secretary-general of the German Central Committee for the Fight against Tuberculosis, interesting and valuable reports are available for a few years with regard to tuberculosis in the Federal German Republic. They bring out strikingly the inroads and high degree of suffering from tuberculosis following World War II. With the population in western Germany less than one-third that of the United States, there were still, in 1953, 107,538 new cases of tuberculosis reported, or as many as were reported here the same year. However, in 1948, in Germany, they numbered as high as 185,622. During the seven years from 1947 to 1953, the number of deaths has been cut by two-thirds. In the same seven years, the death rate has been reduced from 73 to 21 per 100,000 (71 per cent); a decline as rapid, for instance, as has taken place in Canada, although the death rate in Germany is still at a higher level.

If, for a moment, the situation in the United States, Canada, France, and Germany be considered, it will be seen that in the year 1947 in the first three countries, and in 1948 in the last country, a grand total of 116,286 deaths from tuberculosis was reported. In 1953, in the same four countries, the deaths totaled but 47,323, or 68,963 fewer, a reduction in number of 59 per cent, even while the population kept on increasing. For the same years, the new cases reported totaled 402,184 in these four countries, whereas, in 1953, they numbered 285,109, which was 117,075 fewer (29 per cent less). During those few particular years the decline of tuberculosis mortality has been unparalleled; morbidity has also been decreasing, but at little more than half the rate of the former. The greater reduction in the number of deaths than in the number of cases is obviously due to more successful treatment with specific drugs available nowadays.

United Kingdom

In England and Wales, it has taken some time to shake off the impact of World War II; food shortage and destroyed housing continued to lower resistance

(table 3). War prisoners returning with tuberculosis added their burden. The number of new cases reported in 1947, 55,407, was exceeded slightly in 1948 and was still at approximately the same level in 1949. It was only in 1951 and 1952 that some reduction took place and, by 1953, the actual number of new cases of tuberculosis reported in England and Wales, 48,832, was 12 per cent less than in 1947. As a matter of fact, the new cases recorded for 1953 were only a thousand less than in 1940. Striking, however, has been the reduction of tuberculosis mortality. As against 23,551 deaths in 1947, the deaths numbered but slightly more than a third in 1953, namely 8,902. This represents a reduction in number of 62 per cent and, in relation to the population, a decline in the death rate of 64 per cent during the seven years under consideration. It is worth recording that in England and Wales, between 1947 and 1953, in the development of mass roentgenography, more than twelve million members of the civilian population were examined. In 1947, the average number of such roentgenographic examinations per week was 12,513, whereas it was more than four times as great in 1953, namely, 54,166 each week.

In Scotland, new cases of tuberculosis were discovered at almost an identical number in 1947, 1948, and 1949, namely, some ten thousand each year. However, by 1953, the annual number for all forms of tuberculosis was 8,844; since 1947 the number had declined by 13 per cent. At the same time, a much greater rate of progress was being made against tuberculosis mortality. The deaths which at first numbered 4,095, were only 1,341 in 1953, a reduction of 67 per cent. In relation to population, the tuberculosis death rate had come down from 80 to 26 per 100,000, or 68 per cent. For the first time, the death rate in Scotland recently was beginning to approach the lower level it has attained in England and Wales, 26 as compared with 20; whereas, in 1947, it was 80 as against 55.

Great gains have been the result of the highly organized campaign against tuberculosis in Northern Ireland. The new cases in 1953 should be compared with those in 1948 because of a different basis of inclusion previously. During the six years just mentioned, the new cases have fallen in number by no less than 42 per cent. Between 1947 and 1953, the tuberculosis deaths and, consequently, the death rate came down by more than two-thirds (68 per cent).

Eire

In Eire, care must be taken in interpreting the record with regard to tuberculosis. It is the one section of this area, which, when compared with Northern Ireland and England during the period under consideration, has shown some increase in the number of cases, particularly during the years 1947, 1948, and 1949. Two things must be remembered: first, that the higher level in Eire of tuberculosis case rates and of mortality reflect a picture to be found in other parts of the world where industrialization and modern development have been more recent.

It was only at the close of the nineteenth century, namely, in 1898, that the tuberculosis death rate—or one may rather say the tuberculosis epidemic—reached its crest in Eire. Since that time, there has been, although starting from a higher level of prevalence, a rate of progress equal to that in countries just

mentioned, namely, a decline in the death rate of 68 per cent between 1947 and 1953. It has also been common knowledge that during World War II a number of Irish workers went over to England in answer to the increased demands for labor. Many of them came from rural areas where their pursuits previously were agricultural and in the open air rather than in factories and on the "assembly line." It has likewise since been stated that a higher proportion of these were from parts of Eire where many are tuberculin-negative and were not infected until they went to England. Some of these emigrants developed tuberculosis more readily than others long immunized; they returned home to Eire and, as the record shows, during the years of 1947 to 1949 the number of reported new cases rose. Even at the higher level of prevalence, however, the reduction in the case rate of 12 per cent is similar to that in Scotland (12) and close to that in England (14). At the same time, utilizing the newer forms of treatment, the tuberculosis death rate has been brought down by 68 per cent.

Scandinavian Countries

There is particular interest in reviewing the course of tuberculosis in recent years in the principal Scandinavian countries (table 4), for there one finds extremes. In Denmark, the death rate in 1953 was 10 per 100,000 (8 for pulmonary forms only) while in the same year it was 45 in Finland. In Norway, the death rate was 16 per 100,000 population and, in Sweden, 15. At different levels, there has been a great deal of similarity in the rate of progress in reducing tuberculosis mortality in each country: in Denmark, 67 per cent; Norway, 71 per cent; Sweden, 71 per cent; and Finland, 73 per cent. On the other hand, the course of morbidity has not been the same. In Norway, the number of new cases during the seven years under review was reduced by 17 per cent; in Sweden, by 44 per cent; in Denmark, the pulmonary cases were reduced by no less than 50 per cent.

In Finland, figures quoted for new cases cannot easily be compared except for a few years. There was an improved and modified extent of registration in more recent years. Prior to 1951, registration of new cases included only those in the records of the dispensaries of the Finnish Anti-Tuberculosis Association. In 1951, a general reorganization of tuberculosis work in Finland brought the entire population into a unified program directed by the State Medical Board. Despite these difficulties in the reporting, it is worth noting that, between 1947 and 1950 alone, the number of new cases reported fell from 9,245 to 5,935, or 36 per cent.

According to the Tuberculosis Research Office of the World Health Organization (4):

> Tuberculosis mortality in Finland, as in almost every other country, has decreased very rapidly since the second World War, particularly in the younger age groups. However, since a similar pattern is found in countries where BCG has not been used, there seems to be little compelling evidence to support a belief that the nation-wide BCG program (1948–1949) caused much, if any, of the recent precipitous drop in mortality rates. Other factors having a strong influence on tuberculosis mortality have undoubtedly been operating in Finland as almost everywhere.

Improvement in conditions after World War II, availability of powerful antimicrobial drugs lately, and many other perhaps unknown factors have been at play. The authors of the WHO Tuberculosis Research Office study conclude

> . . . that factors other than BCG must have been operating is obvious because the unprecedented drop in mortality among older members of the population cannot have been influenced by the vaccination program in the younger age-groups.

Tuberculosis mortality in Finland is high as compared with other European countries. Before the end of World War I, the death rate from respiratory tuberculosis fluctuated between 250 and 300 per 100,000; by 1953, it had dropped to 56 for males and 27 for females. In 1953, the death rate for all forms of tuberculosis was 45 in Finland, or three times the rate in Sweden and Norway, which were 15 and 16, respectively.

Iceland

In Iceland, an unusually favorable situation with regard to the prevalence of tuberculosis continues to develop (table 5). It is of particular interest because this is one country where, until recently, there was little utilization of BCG as compared with the practice in the Scandinavian countries. The morbidity rate, however, continues to be fairly high, especially when compared with that in Denmark, being three times as great. However, there has been an amazing reduction in the mortality between 1947 and 1953. The number of tuberculosis deaths has been reduced by 80 per cent and the death rate by 83 per cent—the greatest decline reported in any of the different parts of the world under consideration in this review. In 1953, the death rate in Iceland, 9 per 100,000, was but one-fifth of what it still is in Finland. While no reports are at hand with regard to registration of new cases in 1953, still, during the six years between 1947 and 1952, the case rate fell by no less than 49 per cent.

As reported by Sigurdsson and Edwards (5):

> According to the old medical records, tuberculosis appeared to be relatively rare in Iceland nearly eighty years ago. . . . With the turn of the century, people started migrating towards the urban centers, and the ensuing rapid influx to the villages and towns was often accompanied by crowded and unsanitary living conditions . . . tuberculosis mortality increased irregularly, but persistently, to reach a peak above 200 per 100,000 in 1930. Then came a sudden, and precipitous, drop which has continued, almost without interruption, to the present time when over 70 per cent of the population are now considered urban residents.

It is difficult to identify the particular factors most responsible for the continuous decrease of tuberculosis in Iceland; however, several have been at play. Housing, nutrition and health education have all improved in late years and have no doubt been of great importance. Tuberculosis control measures have stressed systematic case finding and isolation of open cases. Ten to 20 per cent of the entire population have been examined each year since 1940; in 1945, 40 per cent of the population were included. There has been systematic tuberculin testing of school children. In 1950, there were 1.7 beds available for each newly

detected case of tuberculosis, or 13 beds per death from tuberculosis. The government pays the cost of sanatorium and hospital care. As a result the White Plague is being "stopped in its tracks."

New Zealand-Australia

Passing practically to the opposite side of the world, namely, to New Zealand and Australia, the reports which were kindly made available for the period under consideration illustrate the universality, at least in the more or less advanced countries, of the tremendous gains recently made against tuberculosis. Between 1947 and 1953 in New Zealand, the number of new cases of tuberculosis reported annually has come down from 1,692 to 1,439 (15 per cent); but, at the same time, the number of deaths was being reduced by 55 per cent. During those particular seven years the case rate fell from 100 to 75; and the death rate, from 31 per 100,000 to 12 (61 per cent).

In the wide continent of Australia, noted generally for its comparatively healthy conditions, the record of tuberculosis in the recent period is also of special interest (table 5). There, too, because of improved forms of treatment possible, mortality from tuberculosis has declined strikingly. There has been, on the other hand, an increase amounting to 25 per cent in the number of new cases recorded annually between 1947 and 1953; during the first year mentioned, 3,971 new cases and, lately, 4,979, or 1,008 more. It should be quickly added, with regard to population, that the post-war period was marked by a continued high natural increase and a resumption of immigration. Whereas, in 1940 the population totaled 7,040,661, in 1953 it was approaching the 9,000,000 mark. It is also likely that, along with the stress of war, the problem of adaptation of the new immigrating groups likewise brought increased tuberculosis problems. However, in relation to the population exposed, the case rate, 52 per 100,000 in 1947, was a comparatively low one. There has been little improvement, as already remarked, in its level and, by 1953, it was still 56. On the other hand, the mortality has been fast declining: 2,261 deaths in 1947 and 974 in 1953. The tuberculosis death rate for the country as a whole therefore came down during that period from 30 per 100,000 to 11 only, a reduction of 63 per cent.

Selected Localities of the United States of America and Canada

Puerto Rico: In a review of the course of tuberculosis in various and different localities, the developments in Puerto Rico are illuminating for both contrast with, and similarity to, what may also be seen in such widely separated places as Australia or, again, in Iceland and in New Zealand (table 5).

First, it should be noted that Puerto Rico suffered, during the nineteen thirties, the highest tuberculosis death rate of any of the different areas under consideration here. In 1930, the rate was 263 per 100,000, and it still stood at 260 by 1940. It was in very recent years that the peak of the tuberculosis epidemic was reached among the people of that island, namely, in 1933, when the death rate was 333 per 100,000. During that decade, there had been a large migration of the population from rural areas to towns and cities, with resultant grave difficulties in find-

ing housing. That period saw the development of a number of slums where contagious diseases spread frightfully.

As related by Pastor and Janer (6), within a year of the appearance of the tuberculosis crest, an intensive campaign against tuberculosis was initiated by the health authorities. An addition of a thousand tuberculosis beds trebled the facilities available, particularly for the isolation and treatment of open cases of tuberculosis. At the same time, a wide case-finding campaign was launched. During the four-year period, 1935–1939, a total of 147,000 persons were examined under the new program with thoroughness in the follow-up of suspects, no less than 125,565 sputum examinations having been made. A number of fully-equipped pneumothorax clinics were organized at key points throughout the island for the treatment of "open" ambulatory cases.

At the same time, application of modern public health measures resulted in a marked lowering of the general mortality in Puerto Rico. It is, therefore, not surprising to see, during the more recent period of 1947–1953, the number of new cases of tuberculosis decline from 6,367 to 5,246 (18 per cent), even while the population was increasing at a high rate. With active and effective treatment of the sick, tuberculosis mortality fell rapidly: 4,160 deaths in 1947 and only 1,046 in 1953. In relation to the population, the death rate can be seen to have dropped from 192 to 47 per 100,000, or by no less than 76 per cent—a proportionate gain tying for second place in the series under review with that made in the Netherlands. Iceland, it will be recalled, enjoyed the greatest reduction: 83 per cent.

New York State-State of Kansas: A review of the tuberculosis record and of general conditions in the states of New York and Kansas in the United States, which are markedly different especially with respect to occupation of their people, confirms further how much the trend of tuberculosis in each of these states has been affected lately by the availability of the antimicrobial drugs for the treatment of this still world-wide plague (table 6).

New York State has the largest population of any in the United States, more than fifteen million; the population of Kansas is almost exactly two million. New York State has an area of 49,576 square miles, whereas Kansas is much more spacious, with 82,276 square miles.

The density of population in the state of New York averages 309 per square mile, rising to as high as 880 in the Borough of Manhattan, an island which forms the central portion of New York City. On that narrow island of 22 square miles, there are two million residents in addition to the hoards of suburbanites and visitors who go there daily for business, work, shopping, or pleasure. In Kansas, the density of population averages 23 per square mile. Preventing the spread in New York City of a communicable disease such as tuberculosis is a herculean daily task.

In the state of New York, 86 per cent of the population reside in urban centers and only 14 per cent in rural areas; whereas, in Kansas, nearly half, namely 48 per cent, still carry on their daily tasks in rural areas, and one-half of the latter are engaged in farming. The state of Kansas produces one-fifth of the

entire supply of the winter wheat of the nation. It should be further noted that, whereas in the state of Kansas only about 4 per cent of the population is non-white, in New York State the latter group comprises 16 per cent of the entire population. There are nearly one million Negroes in New York State. In the New York City area there are 400,000 relatively recently arrived people from Puerto Rico. Industrial development in New York State is both varied and extensive in character. New York City is the financial center of the United States.

As is well known, New York, with its remarkable harbor and transportation facilities, has been, for decades, the principal port of entry of the tremendous number of immigrants to America. Succeeding waves of newcomers—Irish, German, Italian, Jewish, Negroes from the South, and Puerto Ricans—have followed one after the other, each to face most difficult competitive conditions in adapting himself to life in the New World and especially in this part of the United States. As a result, tuberculosis problems have been constant, to be met anew over and over again.

Among the millions of residents in New York City, hardly has tuberculosis been brought under control among the older residents when new arrivals pouring in by thousands require urgent attention. And yet, the big city embraces them all as part of growth and life.

To cope especially with tuberculosis and other allied health problems, highly organized departments of health have been created by the state, municipal, and county authorities. Extensive case-finding campaigns have been carried on regularly, not only among the apparently healthy of the general population but, lately, with state aid, among patients admitted to general hospitals.

All "means tests"[4] for treatment in sanatoriums and for tuberculosis hospital services have been abolished. Generous public relief is granted through departments of welfare. Rehabilitation services are being steadily increased. Slum areas are being eliminated and modern housing projects, aided by the federal, state, and municipal authorities, are underway everywhere.

Opportunities for medical education are extensive. Within New York City alone, there are six schools of medicine, all closely associated with diversified hospital facilities. It was in two of the local institutions, namely, the Sea View Hospital and the New York Hospital-Cornell Medical Center, that the latest available drug for the treatment of tuberculosis, isoniazid, was first utilized.

During the recent seven-year period under consideration, recalling the special conditions of industry and racial groupings in the state of New York, the tuberculosis death rate, which was 38 per 100,000 in 1947, was reduced to 13 by 1953 or but a little more than a third of what it was previously, a drop of 66 per cent (table 6). The number of new cases during those seven years has fallen by 12 per cent, namely, from 12,915 to 11,375. It is necessary to repeat that this has occurred even while a steadily increasing number of cases of tuberculosis was being found among Puerto Ricans recently settling in the New York metropolitan area.

[4] A procedure requiring an applicant to demonstrate inability to pay for treatment before the services can be provided by governmental funds.

Returning to the state of Kansas, it should be stated that there is a well-organized rural health program in that state, that there are many social welfare agencies, and that mental and penal institutions, where tuberculosis often thrives, have all been modernized.

During the seven years from 1947 to 1953, the tuberculosis death rate in Kansas, always low in that comparatively healthy state, has fallen from 17 to only 5 per 100,000, a drop of 71 per cent in just that brief period. Kansas enjoys at the present time one of the very lowest tuberculosis death rates to be found.

Ontario-Quebec: In connection with this series of reports it has been deemed of interest to see—within Canada, for instance—what has been happening in two provinces, greatly different in racial composition and levels of prevalence of tuberculosis, namely, Ontario and Quebec. The people in the first are practically all of Anglo-Saxon or general European descent; the people in the second province are predominantly French-Canadian. As should be expected, the tuberculosis death rate in the Province of Quebec is relatively high, reflecting what is to be expected in a group still fairly close to the time when its occupation was mainly agricultural and the bulk of the people were living in rural sections. Contrariwise, in Ontario are the descendants of people from England and European urban cities who were comparatively "immunized" against tuberculosis much longer ago. In these two provinces, however, parallel changes at two different levels have occurred: the tuberculosis death rate in the English-speaking province has fallen by 76 per cent, and in the French-speaking province by 70 per cent. In Ontario, the very remarkably low death rate of 6 per 100,000 prevailed in 1953; whereas, in Quebec, it was practically two and one half times as great, namely, 20; a similar ratio to that in 1947 when the first had a rate of 25 and, the second, of 66.

NINETEEN-FIFTY: A HALTING YEAR

At the Thirteenth Congress of the International Union Against Tuberculosis in Madrid in September, 1954, Blanco-Rodriguez (7) drew attention to an apparent slow-down, if not a temporary increase, of tuberculosis rates in 1951. He raised the question whether this might not have been a manifestation of a delayed mortality of a number of patients with advanced disease previously treated with streptomycin. The writers of the present paper have, therefore, thought it worth while to inspect more closely the record at hand. Such an inspection would seem to bear out that there was indeed a kind of halting, a "ralentissement" or slow-down, in the decline of tuberculosis at that time.

If one looks particularly at the course of the tuberculosis death rate, it may be seen that during the recent period when, in the United States, the rate was falling three or four deaths per 100,000 population annually, in 1951 it was but two deaths lower than in 1950, namely, 20 per 100,000 against 22. In Sweden, there was no decline at all, the rate remaining at 22. In Denmark, there was some reduction, but of only one death per 100,000. In Switzerland, the death rate remained the same in 1951 as in 1950, namely, 35 as against 35 previously. In Germany, where recovery was rapid, the decline was small: two deaths, 37

against 39; in Austria, likewise, a reduction of but two deaths per 100,000. Actually, in Iceland, the rate in 1951, namely, 21 per 100,000, was one higher than that of 1950 when it was 20. In France, it rose by three deaths, 61 as against 58; likewise, in Italy, 43 as against 40.

If one also studies the figures closely, for instance, of the case fatality among veterans hospitalized on account of tuberculosis by the U. S. Veterans Administration (table 8), the record of 1951, 10.6 per cent, is hardly different from that of 1950, when it was 10.9 per cent. In other words, there was no further gain in this large group of patients during that year. Similarly, at the Sea View Hospital in New York City, the case fatality remained stationary: 27 per cent in 1951 as against 27 per cent in 1950.

In other countries, if one looks again at the reports for 1951—this time in terms of the community case-fatality rate, namely, the ratio of deaths to the new cases reported—it may be seen that in Canada it actually rose to 31 per cent as against 29 in 1950. In Germany, the community case-fatality rate failed to show improvement in 1951; it remained stationary: 15 per cent as against 15 per cent. In New Zealand, the rate went up to 28 per cent compared with 27 per cent the year before. In Ontario, it was higher in 1951: 45 per cent against 41; in the Province of Quebec also, 37 per cent as against 32 per cent.

It must therefore be admitted that a comparatively unusual situation developed about that time; there was no obvious gain against tuberculosis, generally speaking, during 1951. The resumption of the decline in 1952 and 1953 was speeded by the appearance of isoniazid and undoubtedly was aided by the possibility of more successful surgery now that the patients were being brought more safely and quickly to a situation in which surgical therapy could be employed.

* * *

Altogether then, there is a similarity of trend in all of these reports of tuberculosis in various parts of the world, especially during the seven-year period between 1947 and 1953 (table 7). A definite decline in morbidity occurred and there was a still greater reduction of mortality. In such places as England, Wales, and Scotland, and in Eire and France, the case rate has fallen only between 12 and 16 per cent. On the other hand, there are instances, as in Northern Ireland, Germany, Sweden, Iceland, and Denmark, where it has dropped by more than 40 per cent.

The number of tuberculosis deaths has come down everywhere on a tremendous scale during these seven years. Even in France, where they have decreased comparatively least, the reduction has still amounted to 51 per cent; and in Iceland, the deaths dropped by 83 per cent. In most countries with available records, the tuberculosis death rate has been cut from approximately two-thirds and even up to three-fourths during these first seven years of the chemotherapeutic era. In figure 2 is shown graphically the trend in the case rate and death rate from tuberculosis in six widely scattered areas, between 1947 and 1953, namely, in the United States, England and Wales, Norway, Sweden, France, and New Zealand. Recovery from the stress and trials of World War II, improvements

TABLE 7

DECLINE OF TUBERCULOSIS MORBIDITY AND MORTALITY BETWEEN 1947 AND 1953 IN FIFTEEN DIFFERENT COUNTRIES AND THE COMMONWEALTH OF PUERTO RICO

Country	Cases	Case Rate	Deaths	Death Rate
United States	Dec. 28,021 = 21%	Dec. 27 = 29%	Dec. 28,671 = 60%	Dec. 21 = 64%
Canada	Dec. 3,167 = 23%	Dec. 35 = 33%	Dec. 3,639 = 67%	Dec. 30 = 71%
France	Dec. 7,803 = 11%	Dec. 27 = 16%	Dec. 16,020 = 51%	Dec. 42 = 53%
Germany	Dec. 78,084 = 42%	Dec. 181 = 45%	Dec. 19,869 = 66%	Dec. 52 = 71%
England and Wales	Dec. 6,575 = 12%	Dec. 18 = 14%	Dec. 14,649 = 62%	Dec. 35 = 64%
Scotland	Dec. 1,273 = 13%	Dec. 24 = 12%	Dec. 2,754 = 67%	Dec. 54 = 68%
Northern Ireland	Dec. 1,201† = 42%	Dec. 92 = 43%	Dec. 658 = 68%	Dec. 50 = 68%
Eire	Inc.* 660 = 11%	Inc.* 24 = 12%	Dec. 2,510 = 58%	Dec. 84 = 68%
Norway	Dec. 646 = 17%	Dec. 27 = 23%	Dec. 1,221 = 69%	Dec. 40 = 71%
Sweden	Dec. 5,984 = 44%	Dec. 94 = 47%	Dec. 2,472 = 70%	Dec. 37 = 71%
Denmark	Dec. 1,758 = 50%	Dec. 45 = 53%	Dec. 669 = 66%	Dec. 16 = 67%
Finland	Dec. 3,310‡ = 36%	Dec. 92 = 38%	Dec. 4,645 = 72%	Dec. 123 = 73%
Iceland	Dec. 160§ = 43%	Dec. 134 = 49%	Dec. 57 = 80%	Dec. 44 = 83%
New Zealand	Dec. 253 = 15%	Dec. 25 = 25%	Dec. 286 = 55%	Dec. 19 = 61%
Puerto Rico¶	Dec. 1,121 = 18%	Dec. 59 = 20%	Dec. 3,114 = 75%	Dec. 145 = 76%
Australia	Inc.* 1,008 = 25%	Inc.* 4 = 8%	Dec. 1,287 = 57%	Dec. 19 = 63%
New York State	Dec. 1,540 = 12%	Dec. 17 = 18%	Dec. 3,359 = 63%	Dec. 25 = 66%
State of Kansas	Dec. 564 = 59%	Dec. 32 = 63%	Dec. 222 = 69%	Dec. 12 = 71%
Ontario	Dec. 42 = 3%	Dec. 6 = 7%	Dec. 731 = 70%	Dec. 19 = 76%
Quebec	Dec. 1,313 = 24%	Dec. 50 = 34%	Dec. 1,592 = 65%	Dec. 46 = 70%

* In Eire and Australia tuberculosis cases were more numerous in 1953 than in 1947.
† 1953/1948.
‡ 1950/1947.
§ 1952/1947.
¶ Commonwealth.
Note: Dec. = decrease; Inc. = increase.

TABLE 8 (Part 1)

VETERANS ADMINISTRATION, MORTALITY OF HOSPITALIZED TUBERCULOSIS PATIENTS, YEARS 1942–1946, AND 1947–1953

Year	Number Discharged		
	Total	Alive	Dead
1942*	8,272	6,352	1,920 = 23.2%
1943*	8,587	6,664	1,923 = 22.4%
1944*	10,114	7,813	2,301 = 22.8%
1945*	11,725	9,405	2,320 = 19.8%
1946*	11,820	9,444	2,376 = 20.1%
1947*	15,014	12,443	2,571 = 17.1%
1948*	16,906	14,636	2,270 = 13.4%
1949*	17,007	14,646	2,361 = 13.9%
1950†	17,281	15,391	1,890 = 10.9%
1951†	17,040	15,226	1,814 = 10.6%
1952†	16,318	14,908	1,410 = 8.6%
1953†	17,492	16,176	1,316 = 7.5%

* Fiscal year ending June 30.

† Calendar year.

Data refer to cases of pulmonary tuberculosis. Figures by courtesy of the Veterans Administration.

TABLE 8 (Part 2)

TUBERCULOSIS MORTALITY, YEARS 1940–1946, AND 1947–1953

Year	Sea View Hospital New York City			New York Hospital-Cornell Medical Center		
	New* Admissions	All† Deaths	Fatality Ratios	New* Admissions	All† Deaths	Fatality Ratios
			per cent			*per cent*
1940	1,826	558	31	93	7	8
1941	1,773	586	33	104	6	6
1942	1,905	733	38	129	10	8
1943	1,907	844	44	188	10	5
1944	1,525	744	49	154	8	5
1945	1,124	649	58	142	9	6
1946	1,145	560	49	118	12	10
1947	1,286	561	43	81	2	2
1948	1,299	467	36	53	5	9
1949	1,294	406	31	54	5	9
1950	1,540	412	27	50	8	16
1951	1,399	378	27	53	5	9
1952	1,340	314	23	49	1	2
1953	1,252	192	15	48	0	0

* All forms of tuberculosis.

† All deaths whether of new or readmitted patients.

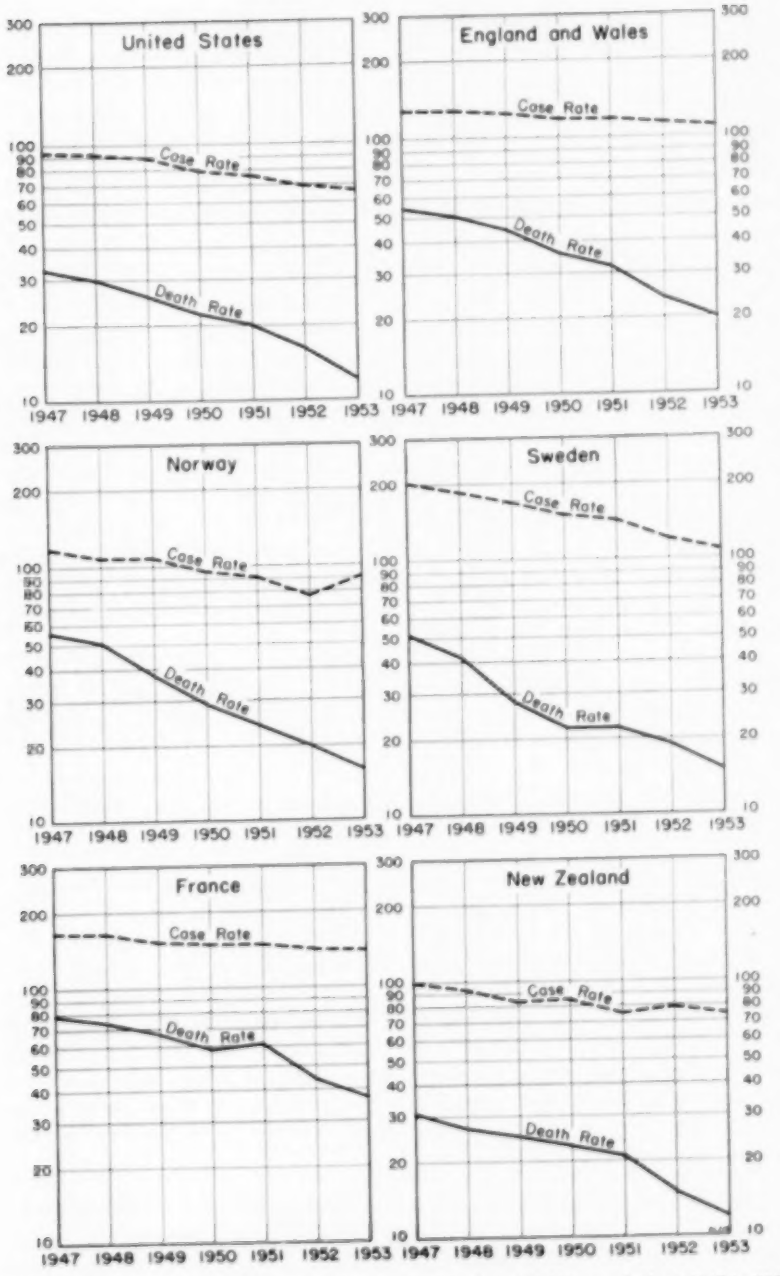

FIG. 2. Tuberculosis morbidity and mortality rates (per 100,000 population) 1947 to 1953.

of socio-economic conditions, intensification of antituberculosis activities have all contributed to a lower incidence of tuberculosis in most of these countries. Nevertheless, it is believed that the availability and use of antimicrobial drugs during the period represent the factor which has been primarily responsible for the greatest reduction in the fatality of the disease ever witnessed in so short a period of time.

Influence of Antimicrobial Drugs on the Treatment of Tuberculosis

As a result of the courtesy of Dr. Robitzek of the Sea View Hospital, Dr. Muschenheim of New York Hospital-Cornell Medical Center in New York City, and Dr. Schneider of the U. S. Veterans Administration, it is possible, from the records of their institutions, to see the immediate effects upon case fatality rates in hospital services where, especially, streptomycin and subsequently isoniazid were first used (table 7) (8). As stated previously, following the initial clinical studies of streptomycin at the Mayo Clinic and at the New York Hospital-Cornell Medical Center, a large-scale test of streptomycin was launched in the latter part of 1946 on hundreds of patients in a joint study by the Veterans Administration, the Army, and the Navy. Prior to 1947, the case fatality rate among tuberculous patients hospitalized by the Veterans Administration had ranged between 20 and 23 per cent; as a matter of fact, it had remained around that level for a number of years. With streptomycin more widely used by the Veterans Administration in 1947, the case fatality rate immediately dropped 3 points to 17.1 per cent, with a further break to 13.4 in 1948.

It was in 1949 that PAS became generally used in the United States as a companion drug for streptomycin in an effort to retard the emergence of drug-resistant tubercle bacilli. With dual-drug therapy, the fatality rate among veterans hospitalized because of tuberculosis came down again, but with a tendency to stabilize around 10 per cent. Finally, in late 1951, came the introduction of isoniazid at the Sea View Hospital by Robitzek and Selikoff and, independently, at the New York Hospital-Cornell Medical Center by McDermott and Muschenheim and their respective associates, all of New York City. Its use in 1952 among patients of the U. S. Veterans Administration resulted in a further lowering of the case fatality, the rate coming down to 8.6 per cent; finally to 7.5 per cent in 1953—practically one-third only of what it was in 1946. It was here in the institutions just mentioned that the antimicrobial drugs saved hundreds of lives. As against 12 deaths at the New York Hospital-Cornell Medical Center in 1946, there were none in 1953; at the Sea View Hospital, there were 560 formerly, 192 lately; among veterans, there were 2,376 then, 1,316 now. As is well known, there was wide publicity given especially to isoniazid, which was likewise developed independently at approximately the same time in West Germany, and there ensued a rush in various parts of the world to employ the drug in the treatment of patients on a wide scale.

The Sea View Hospital and the New York Hospital-Cornell Medical Center

There is historical interest in the conditions and developments at the Sea View Hospital and the New York Hospital-Cornell Medical Center. The former

institution of 1,402 beds is one of the largest institutions for the care of the tuberculous in the world; the latter institution has a limited service employed principally for teaching and research. In appraising the influence of chemotherapy upon recent mortality rates, it is especially at a large institution like the Sea View Hospital that one can see the immediate gains made. The figures for the seven years prior to 1947 are also important as background. It will be noted, first of all, that, annually, the fatality ratio in relation to new admissions was formerly very high; as a matter of fact, there had even been a tendency for a few years for this condition to worsen. In 1945, more than half of the patients admitted to Sea View died; the fatality rate that year reached 58 per cent. It should be borne in mind, however, that at this particular institution a high proportion of far advanced cases of tuberculosis were being sent after selection from other admitting hospital emergency services. Then, in those years there was an increasing number of colored patients and of comparatively recent arrivals from Puerto Rico. These two groups of patients still display more rapidly progressive and extensive tuberculosis than the older groups in New York City, for example, those of Italian or Jewish stock.

At the Sea View Hospital, in 1947, the case fatality ratio was still 43 per cent. With streptomycin at hand, material improvements were immediately obtained. The case fatality rates fell to 36 per cent in 1948 and to 31 per cent in 1949, but stabilized at 27 per cent in 1950 and 1951. It was in the latter part of 1951 that isoniazid was first used in a group of approximately 90 patients. As pointed out by Robitzek and Selikoff (9), "all patients suffered from extensive bilateral, far-advanced, active, progressive, caseous-pneumonic tuberculosis and in the pre-therapy period had failed to show improvement; they really were judged hopeless; all persistently had positive sputum. Ten of them had tuberculous laryngitis and many had extra-pulmonary or non-pulmonary disease."

In 1952, when the patient-census averaged 1,544, a great majority (ultimately more than 1,200 patients) were receiving isoniazid therapy. At the end of 1953, a still higher proportion, more than 90 per cent of the patients, were receiving isoniazid. The case fatality rate immediately came down to 23 per cent in 1952 and, in 1953, to 15 per cent when, therefore, it was practically only one-third of what it had been in 1947. The much higher fatality ratios in the Sea View Hospital, as already mentioned, were in great part due to the racial composition of the patients and their very serious condition. At New York Hospital-Cornell Medical Center, reference should be made to the relatively more numerous deaths in the year 1950; of the 8 which occurred, 5 were among patients who had been there for less than one month. In 1953, there were no deaths.

Prevalence of Infection—Children Aged Fifteen

The third index, previously mentioned, which may be used with reference to the incidence or prevalence of tuberculosis is the extent of infection as revealed by tuberculin tests. It is obvious, in places or areas where tuberculosis morbidity and mortality are being brought down to very low levels, that there shall be an increasing need and use of the tuberculin test. It is therefore of importance to begin recording and bring to general attention such reports of the results of these

TABLE 9

PREVALENCE OF TUBERCULOUS INFECTION AT AGE FIFTEEN*
In Various Countries or Cities in Recent Years†

Country	Male	Female	Both
	per cent	*per cent*	*per cent*
Asia			
Korea (1953)			
Entire campaign	61	52	60
Seoul	82	79	82
Taiwan (Formosa) (1951–52)			
Urban communities	—	—	66
Rural communities	—	—	40
Ceylon (1949–51)			
Western Province	—	55	60
Colombo	—	—	63
India (1949–51)			
Calcutta	—	—	72
Bombay	—	—	77
Aden Colony (1952)			
Entire campaign	—	—	69
Middle East			
Lebanon (1949–50)			
Beirut and suburbs	15	12	13
Syria (1950)			
Entire campaign	45	40	43
Damascus	40	36	38
Israel (1949–50)			
Entire campaign	34	31	33
Jerusalem, urban	27	23	25
Tel-Aviv	30	30	30
Jews, born in Israel	—	—	23
Jews, immigrants	—	—	44
Palestine Arabs (1949)			
Refugees, Transjordan, Gaza, et cetera	34	30	—
Egypt (1950–52)			
Entire campaign	54	50	52
Nine urban districts	57	46	—
Nine rural districts	53	49	—
Cairo governorate, age 14	53	43	—
Suez governorate	52	50	—
Port Said	—	—	48
North Africa			
Algeria (1949)			
Entire campaign	52	49	51
Cities	68	64	—
Rural communes	48	45	—
Algiers	64	59	—
Morocco (1949–51)			
"Cities"	74	64	—
Rural districts	45	40	—
Casablanca	81	75	—
Fès	86	83	—
Tangier (1950)			
City	78	72	—
Rural district	47	28	—
Tunisia (1949–51)			
Entire campaign	57	49	53
Bizerte			
Urban	56	38	—
Rural	49	41	—
Tunis			
Urban	72	70	—
Rural	57	45	—
Europe			
Malta (1950)			
Entire campaign	30	29	29
Urban localities	49	47	48
Rural localities	23	21	22
Gozo Island	17	19	18
Greece (1948–51)			
Entire campaign	34	34	34
Cities, over 100,000	55	53	54
Rural areas	25	27	26
Heraclion	21	19	—
Athens-Piraeus	54	53	—
Salonica	57	54	—
Crete	—	—	18
Yugoslavia (1948–50)			
Entire campaign	59	59	59
Fifty-one urban areas	—	—	65
Fifty-one rural areas	—	—	58
Slovenia	36	36	36
Macedonia	50	57	53
Serbia	65	66	66
Czechoslovakia (1948–49)			
Czech provinces	43	44	44
Slovakia	55	58	57
Prague	53	50	—
Bratislava			
Urban	52	56	—
Rural	47	60	—
Hungary (1948–49)			
Budapest	—	—	60
Austria (1948–50)			

TABLE 9—*Continued*

Country	Male	Female	Both	Country	Male	Female	Both
	per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
Entire campaign	33	33	33	Eire (1951–52)§			
Ten urban districts	37	37	37	Two urban communities	—	—	68
Ten rural districts	34	34	34	Four rural parishes	—	—	18
Vienna	42	43	—	Sligo			
Displaced children, age 12	51	50	—	Urban	—	—	40
Germany (1948–49)				Rural	—	—	14
Hesse only	—	—	49	Cork	—	—	94
Poland (1948–49)				America			
Entire campaign	66	68	67	Ecuador (1950–51)			
Kracow province	60	62	61	Entire campaign	51	48	49
Lublin province	67	70	68	Urban areas	61	58	—
Gdansk, urban	73	75	—	Rural areas	41	38	—
Warsaw	79	78	78	Quito	63	62	—
Lodz	83	84	84	Guayaquil	77	75	—
Poznan	85	85	85	Mexico (1950)			
England and Wales (1949–50)‡				State of Hidalgo	—	—	46
				State of Tamaulipas	—	—	51
Urban England, south	—	—	38	Vera Cruz	—	—	52
Rural England and Wales	—	—	53	New York City (1950–52)¶			
Urban England, N. and Wales	—	—	51	Queensboro, white 9%, colored 13%	9	8	9
London, four districts	38	34	—	Manhattan, Bronx, Brooklyn	—	—	12

* Positive reactors to tuberculin test.

† Based in part upon reports of "The International Tuberculosis Campaign" and the Tuberculosis Research Office, World Health Organization, Copenhagen, Denmark.

‡ National Tuberculin Survey, England and Wales.

§ National Tuberculosis Survey, Ireland.

¶ Survey by Queensboro Tuberculosis and Health Association, and by Department of Health, City of New York.

tests in various places, especially before their value is impaired by the widening campaigns with BCG vaccination.

Because of the almost universal prevalence of infection in adult life in certain parts of the world, it is particularly during childhood that more significant records on the level of infection can be noted for historical and comparative purposes. A practical age for comparisons would seem to be around fourteen or fifteen, especially in localities where there are compulsory educational requirements for children and they are more likely to be accessible in groups. It is also of importance that the tuberculin reaction have wider use as a test now that, with modern methods of treatment of active disease, it is realized that it is not necessarily the chronologic age of the patient which is a determinant factor in tuberculosis but, rather, the age of the infection. Were tuberculin testing done

more frequently and records kept, it could play an important part for more effective and early treatment. As a matter of fact, studies are already under consideration for the active treatment of recent infection or of primary tuberculosis.

Comparatively recent reports of the International Tuberculosis Campaign (10), to which the World Health Organization provided technical guidance and assistance, are a rich source of information on results of tests for tuberculous infection in various countries. Furthermore, these tests were performed under supervised methods and their results are, therefore, unusually comparable. They were done, it will be remembered, in anticipation of vaccination with BCG of large groups, especially of children. It may also be recalled that they cover literally millions of tuberculin tests (38,000,000) "upon children and young adults."

Skimming briefly from nation-wide tuberculin surveys in various countries, selected figures (table 9) disclose the prevalence of infection in the nineteen fifties at age fifteen among boys and girls. In Korea, Formosa, Ceylon, India[5] (where more than 4,000,000 children and young adults of various ages were tested) and in Aden Colony, except in rural areas, from 60 to 75 or 80 per cent of the boys and girls are already infected with tuberculosis at the age of fifteen.

In the Middle East, a variety of interesting reports are at hand. Comparatively lower rates of infection prevail, some as low as 13 per cent in Lebanon, or a rate of 23 per cent among the native Jewish children in Israel. However, among those of immigrant Jewish people, the rate is twice as high, 44 per cent. Among Arab children in camps for refugees, a rate of 32 per cent was found; whereas, in Syria it rose to 43 per cent. In the Djebel Druze district, a comparatively lower rate, namely, 26 per cent, prevailed among boys and girls fifteen years of age. In Egypt, where some 4,373,000 children and young adults were tested, the infection rate at fifteen was approximately 50 per cent, being usually higher among boys than among girls.

In North Africa, Algeria, and Morocco, in each place, more than two and a half million young people were tuberculin tested. In these two countries and in Tangier and Tunisia, the infection rate in the cities, even at age fifteen, was between 60 and 70 per cent, rising to 81 per cent among boys in Casablanca and to 86 per cent in Fēs. For Casablanca city, separate figures on tuberculin sensitivity are available for Moslem, Israelite, and European schoolchildren. Among the last-named, at age fifteen, 42 per cent reacted; the children in the Israelite schools showed 69 per cent positive; and in the Moslem schools, 86 per cent. Here, in North Africa, especially in rural sections, the much lower infection rate among girls than among boys should be noted. In the rural section of Tangier, the first showed only 28 per cent infected at age fifteen, whereas the boys were 47 per cent infected. Similarly, in Bizerte, 41 per cent of the girls reacted positively, and 49 per cent of the boys. Veiling the face of the Moslem girl may well limit opportunity for spread of infection.

[5] According to the WHO Tuberculosis Research Office, "In some areas (of India) nonspecific tuberculin sensitivity is so strong it cannot be effectively distinguished from specific sensitivity."

In Malta, comparatively low rates of infection with tuberculosis were found among boys and girls; also, in Greece, where 1,600,000 of various ages were tested, however, the infection rate in the cities rose to 55 or more per cent. In Yugoslavia, where more than 3,000,000 children and young adults were tested, a most extensive BCG vaccination campaign was conducted and marked variations in infection were found at age fifteen: 36 per cent in Slovenia, but 65 per cent in urban areas. Here the tendency for infection rates to be higher among girls than among boys was noted.

In Montenegro, the infection rate was low, 40 per cent; but it was more than 60 per cent in Bosnia-Herzegovina; in Croatia, 61 per cent; and, in Serbia, 66 per cent. The excess in the female sex is to be found also in Czechoslovakia, where very large numbers of children and young adults were tuberculin tested: 3,300,000; and, in Poland, 4,700,000. In Czechoslovakia, the infection rate was much lower in the Czech provinces (44 per cent) than in Slovakia (57 per cent).

In Poland, some of the highest tuberculosis infection rates prevailed: the rate for both boys and girls aged fifteen was 78 per cent in Warsaw; in Lodz, 84 per cent; and, in Poznan, 85 per cent. In general, the rates among girls were slightly higher than among boys.

The widespread BCG campaigns in France or in the Scandinavian countries have deprived us of this index on the prevalence of infection, except in Iceland where it was attempted only lately. For years, schoolchildren, seven to thirteen years of age, have been tuberculin tested on a comparatively broad scale in Iceland. In 1931, approximately 32 per cent reacted positively. In 1940, practically a decade later, the infection rate was reduced by half, namely, to 16 per cent; and, in 1950, again it was down to 8.6 per cent. BCG vaccination has not been advised in Iceland on the scale originally planned because of the rapid decline in the infection, morbidity, and mortality rates.

The National Tuberculin Survey of 1949–1950 in England and Wales (11) brought out the interesting information that in rural areas, because of failure to pasteurize milk as is now generally done in the cities, children in the countryside of England and Wales had a higher infection rate, namely, 53 per cent, compared with rates between 38 and 51 per cent in urban areas. The children in four boroughs of London had rates averaging 38 per cent for boys, and 34 per cent for girls, fifteen years old. Mention, however, should be made here of the recent survey in the nearby borough of Edmonton, Middlesex (12) (a working-class district where serious overcrowding is common), where the tuberculin testing of children in the schools showed, at age fifteen, positive reactors among no less than 66 per cent of them.

In Eire (13), the recent limited tuberculosis surveys bring out, as suspected, the rarity of infection among boys and girls in rural areas, namely, rates as low as 12 to 18 per cent; but on the other hand, high in urban communities. The low indices in important areas of Eire and, therefore, limited contact with infection at home explain the marked susceptibility to progressive disease when Irish workers from such rural sections emigrate to crowded centers of population in England or in the United States.

Tuberculin Reactors in North and South America

In America, information on a nation-wide scale concerning infection rates is not readily available although, especially in the United States, any number of local tuberculin surveys have been conducted. Even so, during the period under consideration, it is interesting to see the reports, for instance in Ecuador, where nearly 650,000 children and young adults were tuberculin tested during 1950 and 1951. The infection rate in rural areas at age fifteen was approximately 40 per cent, but in Quito and Guayaquil it ranged between 60 and 75 per cent.

In Uruguay (14), more than 200,000 children and young persons were tuberculin tested between 1948 and 1951 in fifteen different departments of the country; 35 per cent of those aged fifteen reacted positively.

In Mexico, rates averaging approximately 50 per cent were found; even in the city of Vera Cruz, the rate was 52 per cent only among boys and girls aged fifteen.

In the United States, unusually low rates of infection are now found to prevail in New York City, the largest center of population with more than 8,000,000 residents; especially in Manhattan, where extreme overcrowding prevails in poorer sections. At the same time, it must be recalled that more than 1,200,000 Negroes and Puerto Ricans reside in that great city. And yet, among boys and girls fifteen years of age, residing in the boroughs of Manhattan, Bronx, and Brooklyn—the densely populated sections of the city—only 12 per cent reacted positively according to Robins and associates (15). As a matter of fact, this is less than half of what the rate was but a few years previously (28 per cent). In the residential borough of Queens, with a population of more than a million and a half, on an average, only 9 per cent of boys and girls fifteen years old have been found to react.

Low Infection Rate Among U. S. Navy Recruits

The unique situation, now reached in the United States, with regard to low infection rates may be more closely studied in authoritative recent reports (16), especially among young men, aged seventeen to twenty, inducted into the United States Navy and Marine Corps. It should be noted in this connection that these recruits came from all parts of the United States: the populous East or the more sparsely settled sections of the West Coast, not to mention those living in the mid-West urban centers (table 10, part 1). The favorable condition of the recruits (only 10.6 per cent reacted positively to tuberculin in 1949 and 1950) is strikingly brought out by contrasting the results of similar tuberculin testing in a group of service inductees in England, Wales, and Scotland at the time of the National Tuberculin Survey by the Medical Research Council. In the latter group were included some 3,500 servicemen eighteen to twenty years of age at entry; 66 per cent, or two-thirds of them, reacted positively to tuberculin.

Further detailed figures are at hand by courtesy of the Surgeon-General of the United States Department of the Navy, permitting the comparison of the infection figures on an annual basis from 1949 to 1954. During these six years

TABLE 10 (Part 1)

RESULTS OF TUBERCULIN TESTS IN BRITISH AND AMERICAN MILITARY RECRUITS, 1949 AND 1950

Group	Number Tested	Positive Reactors	
		Number	Per Cent
England, Wales and Scotland*:			
Service men on entry, 18–20 years	3,450	2,264	65.6
United States:†			
Navy and Marine recruits, 17–20 years	157,081	16,711	10.6

Reactors, English, 64.4%; Welsh, 66.7%; Scotch, 75.4%.

Test: British, tuberculin jelly-test = Mantoux 10 T.U.; American, 0.0001 mg. PPD.

* National Tuberculin Survey, Medical Research Council.

† Figures by courtesy, Bureau of Medicine and Surgery, United States Department of the Navy.

TABLE 10 (Part 2)

RESULTS OF TUBERCULIN TESTS* IN RECRUITS AND MIDSHIPMEN†, UNITED STATES NAVY AND MARINE CORPS, 1949–1954

Year	Total Tested	Type of Reaction		
		Negative	Doubtful	Positive
1949	44,803	40,510	324	3,969 = 8.9%
1950	112,728	99,151	835	12,742 = 11.3%
1951	278,741	242,948	6,933	28,860 = 10.4%
1952	268,238	234,547	6,466	27,225 = 10.1%
1953	136,920	128,593	1,034	7,293 = 5.3%
1954	152,605	144,200	1,313	7,092 = 4.6%

* 0.0001 mg. PPD.

† Seventeen through twenty years of age.

Figures by courtesy, Bureau of Medicine and Surgery, United States Department of the Navy.

nearly one million young men, white and colored, were tuberculin tested by the same authority. Up to 1952, the proportion who reacted positively oscillated between 9 and 11 per cent. In 1953, it was only half of what it was before, 5.3 per cent. And, by 1954, only 4.6 per cent of these young Americans could be shown to be infected with tuberculosis. It is difficult, therefore, to restrain from repeating the observations of a responsible official of the United States Public Health Service, in the light of the situation here, who said, "Why should we now infect our youth with tuberculosis—BCG?"

* * *

Another point which can well be made in connection with the current discussion of the influence of the antimicrobial drugs on tuberculosis is that, even though there are occasional disappointments in their use in the treatment of tuberculosis, it is becoming obvious from the declining infection rate that not only are mortality and morbidity being reduced but, at the same time, the num-

ber of infectors remaining in the community must be fewer in number than previously.

Summary

During the seven years from 1947 to 1953 the most rapid decline in tuberculosis mortality the world has ever seen has taken place.

In fifteen countries and the Commonwealth of Puerto Rico for which both mortality and morbidity reports are available, the fall in the death rate has ranged from 53 per cent in France to 83 per cent in Iceland.

Morbidity reports show a lesser rate of reduction, the case rate being now 20 per cent lower in five of the fifteen countries and one commonwealth referred to above; but, there is record of an actual increase during the period under consideration having occurred in Eire; perhaps, also, in Australia.

The acceleration lately in the fall of the tuberculosis death rate is due primarily to improvement in the treatment of the disease because of the availability of antimicrobial drugs, such as streptomycin, para-aminosalicylic acid, and isoniazid, along with more successful surgery.

The ultimate measure of progress against tuberculosis should be the absence of infection. Tuberculin tests in various parts of the world show that boys and girls at age fifteen still react positively from 12 per cent in Lebanon or 18 per cent in rural Eire to 85 per cent in Polish cities. In 1954, among some 150,000 recruits in the United States Navy and Marine Corps, 95 per cent reacted negatively to the tuberculin test.

Finally, because of the sharpness in the decline of tuberculosis mortality, it would be unwarranted to conclude that tuberculosis is no more a major health problem. Taking only the United States, the British Isles, France, and Germany in 1953 alone, 340,416 new cases of tuberculosis were reported. If in addition to these cases, account be taken of old and previously known cases (conservatively estimated at three times the new cases), it can readily be seen that in just these four countries there were, that year, more than one million known cases of active tuberculosis.

Sumario

¿Adónde Tuberculosis?—Los Primeros Siete Años de la Era Antibiótica, 1947–1953

Durante los siete años transcurridos de 1947 a 1953 ha tenido lugar la baja más rápida de la mortalidad tuberculosa.

En quince países y en el Estado Libre Asociado de Puerto Rico para los que se cuenta con datos tanto de mortalidad como de morbidad, el descenso de la mortalidad ha variado de 53 por ciento en Francia a 83 por ciento en Islandia.

Las estadísticas de morbidad muestran una tasa menor de reducción, siendo hoy día el índice de casos 20 por ciento más bajo en cinco de los quince países y en le estado libre asociado mencionados, pero hay datos de un aumento agudo en Irlanda durante el período bajo consideración; y quizás también en Australia.

La reciente aceleración de la baja de la mortalidad tuberculosa se debe primordialmente al perfeccionamiento del tratamiento de la dolencia por contarse con drogas específicas, tales como estreptomicina, ácido para-aminosalicílico y las niacidas, a la vez que al mayor éxito de la cirugía.

La demostración definitiva del adelanto logrado contra la tuberculosis debe ser la falta

de infección. Las pruebas tuberculínicas ejecutadas en varias partes del mundo revelan que niños y niñas de quince años de edad todavía reaccionan positivamente a la tuberculina en una proporción que varía de 12 por ciento en el Líbano o 18 por ciento en los distritos rurales de Irlanda a 85 por ciento en las ciudades polacas.

En 1954, entre 150,000 reclutas de la Armada y del Cuerpo de Marinos de los Estados Unidos, 95 por ciento reaccionaron negativamente a la prueba de la tuberculina.

Por fin, no estaría justificado deducir, por el brusco descenso de la mortalidad tuberculosa, que la tuberculosis ya no constituye un problema de primera magnitud. En los Estados Unidos, las Islas Británicas, Francia y Alemania, solamente en 1953, se denunciaron 340,416 casos nuevos de tuberculosis. Si, además de éstos, se consideran los casos antiguos y ya conocidos—que se calcula conservadoramente son el triple de los casos nuevos—puede notarse fácilmente que sólo en esos cuatro países, había en dicho año más de un millón de casos conocidos de tuberculosis activa.

Resume

Où en est la tuberculose? les sept premières années de l'antibiotique, 1947–1953

Au cours des sept années de 1947 à 1953, le déclin le plus rapide de la mortalité tuberculeuse s'est produit.

Dans quinze pays et e'état de Puerto Rico pour lesquels on dispose à la fois de rapports sur la mortalité et la morbidité, la chute du taux de mortalité s'échelonne entre 53% en France et 83 pour cent en Islande.

Les statistiques de morbidité montrent un taux de réduction plus bas, le taux des cas de tuberculose étant maintenant réduit de 20 pour cent dans cinq des quinze pays et e'état de Puerto Rico mentionnés; toutefois, dans la période considérée, on a enregistré un accroissement aigü en Eire, et peut-être aussi en Australie.

L'accélération récente du taux de mortalité de la tuberculose est principalement due à l'amélioration du traitement de l'affection par les médicaments spécifiques dont on dispose, tels que streptomycine, acide paraaminosalicylique et niazides, en même temps que par l'emploi de procédés chirurgicaux plus favorables.

La mesure ultime des progrès contre la tuberculose doit être l'absence d'infection. Les tests à la tuberculine, dans les diverses parties du monde, montrent que les garçons et les filles âgés de quinze ans ont encore une réaction positive à la tuberculine, qui varie de 12 pour cent au Liban ou 18 pour cent en Eire rural à 85 pour cent dans les villes de Pologne.

En 1954, sur 150.000 recrues de l' "United States Navy Marine Corps", 95 pour cent des réactions à la tuberculine étaient négatives.

Enfin, le déclin brusque de la mortalité par tuberculose ne permet pas de conclure que la tuberculose a cessé d'être un problème sanitaire majeur. Aux États-Unis, dans les Iles Britanniques, la France et l'Allemagne, pour 1953 seulement, 340.416 nouveaux cas de tuberculose ont été enregistrés. Si, en plus de ceux-ci, on tient compte des cas anciens reconnus antérieurement—qu'une évaluation modérée porte au triple des cas nouveaux—il est facile de voir que, pour ces quatre pays seulement, il y avait cette année-là plus d'un million de cas reconnus de tuberculose en activité.

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PULMONARY FUNCTION BEFORE AND AFTER RESECTION OF TUBERCULOUS LUNG SEGMENTS[1, 2]

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INTRODUCTION

Changes in pulmonary function following uncomplicated lung resection are commonly believed to be proportionate to the amount of tissue removed. Various writers appear to disagree, however, with respect to the direction and degree of these changes.

Smith, Siebens, and Storey (1) studied fifty-one patients who had resections for bronchiectasis and concluded that the operation produced a ventilatory loss proportional to the extent of resection. Woodruff, Merkel, and Wright (2) pointed out that it is the amount of healthy lung removed which determines the degree of impairment. Frequently, when excision is limited to a contracted diseased wedge, segment, or lobe, very little reduction in functional capacity results. Kelley and Pecora (3), in a study of forty-one resections for tuberculosis, reported a definite improvement in maximum breathing capacity (MBC) with removal of two, three, or four segments, a loss appearing only after excision of more than four segments. Landis and Weisel (4) also reported gains as well as losses in function following small segmental and wedge resections for tuberculosis. Etsten, Overholt, Walker, and Reynolds (5), in a postoperative study of resections for bronchiectasis, found that the maximum breathing capacity tended to approach the predicted level in the uncomplicated cases in direct relation to the number of healthy segments preserved.

The influence on postoperative pulmonary function of a space-filling thoracoplasty performed during, or at an interval after, resection is not well defined. Woodruff and associates (2) state that a tailoring thoracoplasty has little effect on function.

It was the purpose of the present study to determine the relationship between function change and amount of lung tissue removed and to observe the possible effect of a staged space-filling thoracoplasty.

MATERIALS AND METHODS

Clinical Material

Seventy-four patients who had unilateral resections for pulmonary tuberculosis between November, 1949, and December, 1954, were selected for study.

[1] From the Surgical Service and The Pulmonary Physiology Laboratory, Veterans Administration Hospital, Rutland Heights, Massachusetts.

[2] Presented before the Medical Session, as part of *Section 5H*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 25, 1955.

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TABLE 1

PULMONARY FUNCTION DATA ON 74 PATIENTS WITH UNILATERAL RESECTIONS FOR TUBERCULOSIS*

Group		Number of Cases	Ventilatory Tests				Bronchospirometry					
			MBC† l/min. (Mean and Range)		VC‡ ml. (Mean and Range)		Per cent Ventilation Operated Side (Mean and Range)		Per cent VC Operated Side (Mean and Range)		Per cent Oxygen Uptake Operated Side (Mean and Range)	
			Before	Change	Before	Change	Before	Change	Before	Change	Before	Change
1 segment	A	8	130.1 (97:173)	+1.5 (−9:+13)	4,212 (3,450:5,400)	−569 (−50:−1,400)	45.8 (32:51)	−4.2 (−19:+11)	45.4 (28:52)	−9.4 (−1:−22)	42.9 (30:52)	−2.3 (−20:+8)
2 segments	A	5	119.0 (77:169)	+2.4 (−42:+48)	3,750 (2,900:4,600)	−830 (−50:−1,200)	48.0 (40:57)	−6.0 (−3:−9)	44.8 (38:49)	−8.8 (−3:−14)	43.8 (26:53)	−7.8 (−17:+6)
	B	3	113.7 (103:134)	−7.7 (−28:+11)	3,867 (3,650:4,150)	−950 (−500:−1,250)	54.3 (49:59)	−15.0 (−37:+3)	51.7 (40:61)	−13.0 (−1:−25)	58.0 (48:71)	−20.3 (−5:−49)
3 segments	A	14	126.7 (77:163)	−14.9 (−48:+27)	4,089 (2,700:5,300)	−911 (−100:−1,600)	50.4 (39:67)	−6.0 (−22:+5)	47.9 (35:57)	−10.2 (−2:−22)	47.8 (39:59)	−4.6 (−24:+10)
	B	15	122.9 (85:193)	−16.5 (−45:+27)	3,970 (3,100:5,200)	−867 (−150:−1,750)	57.1 (37:75)	−9.9 (−22:+5)	53.9 (43:65)	−14.2 (0:−24)	50.7 (26:75)	−13.0 (−32:+10)
	C	3	133.0 (89:163)	−13.3 (−4:−20)	3,317 (3,050:3,600)	−167 (−600:+200)	58.0 (50:68)	−4.0 (−8:+3)	53.3 (39:76)	−14.0 (−2:−34)	46.7 (32:64)	−12.7 (−2:−31)
4 to 5 segments	A	6	133.3 (85:156)	−12.7 (−51:+6)	3,492 (2,500:4,450)	−750 (−400:−1,500)	47.7 34:58)	−6.3 (−18:+4)	43.0 (36:56)	−9.2 (−25:+18)	40.7 (25:58)	−5.7 (−30:+27)
	B	8	107.1 (70:154)	−16.8 (−42:+16)	3,381 (2,350:4,300)	−744 (−450:−1,100)	44.0 (16:59)	−6.8 (−18:+1)	40.8 (13:51)	−8.4 (−5:−14)	40.1 (11:54)	−8.6 (−2:−17)
	C	3	124.3 (84:149)	−10.3 (−19:+5)	2,650 (1,850:3,150)	−150 (−450:+50)	32.3 (21:51)	+9.6 (+9:+10)	32.7 (23:46)	−3.0 (−10:+2)	29.3 (21:42)	−2.3 (−13:+6)

6 to 7 segments	A	2	160.0 (159:161)	−16.5 (−33:0)	4,450 (4,400:4,500)	−1,175 (−1,050:−1,300)	66.5 (52:81)	−19.0 (−10:−28)	57.0 (48:66)	−24.5 (−14:−25)	51.0 (50:52)	−19.5 (−17:−22)
	B	1	107.0	−11.0	2,750	−550	34.0	+6.0	30.0	+15.0	39.0	+6.0
	C	1	67.0	−21.0	2,750	−550	49.0	−32.0	43.0	−7.0	26.0	−8.0
10 segments	B	4	95.0 (59:132)	−24.2 (−7:−33)	3,412 (3,100:3,750)	−1,463 (−1,400:−1,500)	32.3 (26:47)	−32.3 (−26:−47)	28.5 (16:35)	−28.5 (−16:−35)	22.3 (14:31)	−22.3 (−14:−31)
	C	1	82.0	−1.0	1,900	+100	10.0	−10.0	6.0	−6.0	0	0

* Subgroup *A*—no thoracoplasty; Subgroup *B*—post-resection thoracoplasty; Subgroup *C*—pre-resection thoracoplasty
† MBC—maximum breathing capacity
‡ VC—vital capacity

Seventy-three of the patients were males and their ages varied from 21 to 60 years, with a mean of 33.1 years. Thirty-five patients had only the resection procedures, 31 had space-filling thoracoplasties as a separate operation after the resection, and 8 had had surgical collapse procedures at some time prior to the resection. The amount of lung tissue excised varied from one segment to an entire lung; three to five segments were removed from most of the patients.

Many variables which might have some influence on the function results exist in this group of patients. During the period of study, improvements in chemotherapy, operative technique, and the methods of pre- and postoperative management took place. Different surgeons operated with minor variations in technique. Of necessity, these variables had to be accepted. Patients with major complications were not included.

Methods

Ventilatory measurements, including maximum breathing capacity, walking ventilation, and vital capacity, as well as bronchospirometry, were performed on all patients before surgery, in most cases within two weeks of the operation. These tests were repeated on an average of 5.3 months after surgery. Ten patients were studied from one to two months postoperatively; in the remaining 64, the interval after surgery was 2 to 33 months.

Ventilatory tests on all but 7 patients were performed by the same technician. The same equipment and methods were used for all tests.

Maximum breathing capacity was performed with the subject in the sitting position breathing room air for 30 seconds through a low resistance valve (Hans Rudolph). The expired air was collected in a meteorologic balloon and the volume measured in a Tissot spirometer. The maximal of three efforts corrected for BTPS[4] was reported in liters per minute.

Vital capacity was measured directly on a Collins Vitalometer with the subject in the sitting position. The best of three efforts was recorded in milliliters.

Walking ventilation was performed by the method described by Warring (6). The subject walked for three minutes at the rate of 180 feet per minute, breathing room air through a low resistance valve. The expired air was collected in a meteorologic balloon and measured in a Tissot spirometer. The result, corrected to BTPS, was expressed in liters per minute.

Bronchospirometry was performed on fasting subjects premedicated with pentobarbital, atropine sulfate, and morphine sulfate or Demerol® in appropriate doses. A double-lumen flexible rubber catheter was introduced with the aid of a laryngeal mirror after satisfactory topical anesthesia was obtained with Pontocaine® 1 per cent oropharyngeal spray, and 0.25 per cent tracheal instillation. A Gebauer (7) catheter was used for the first 14 patients; the remaining 60 patients were studied with a Carlens (8) catheter. Correct positioning of the catheter was confirmed in every case by roentgenography, fluoroscopy, or auscultation. The subject, in the supine position, breathed an oxygen-rich mixture from a McKesson twin recording spirometer. Two three-minute tracings were obtained at each examination. Ventilation rate, oxygen uptake, and lung volume subdivisions were measured directly, and the per cent contribution to the over-all function by each lung was computed. Values for the per cent ventilation, per cent vital capacity, and per cent oxygen uptake contributed by the operated side were selected for analysis.

RESULTS

The pulmonary function measurements are summarized in table 1. It seemed advisable, as a first step, to separate the patients into subgroups *A*, *B*, and *C*,

[4] Body temperature, ambient pressure, and saturated with water vapor at body temperature.

dependent on whether or not the patient had had a thoracoplasty and whether it was performed before or after resection.

In order to evaluate the influence of the thoracoplasty, subgroups *A* (no thoracoplasty) and *B* (thoracoplasty performed after excision) were compared in those patients who had two, three, or four to five segments removed. The results of this comparison are graphically illustrated in figures 1, 2, and 3. It is apparent that the mean changes were essentially the same whether or not a thoracoplasty was performed. The few patients in subgroup *C* (previous thoracoplasty) were omitted from the comparison figures; the changes following resection in this subgroup were very similar to those observed in subgroups *A* and *B*. Since statistical analysis confirmed these impressions, it was justifiable to combine all three

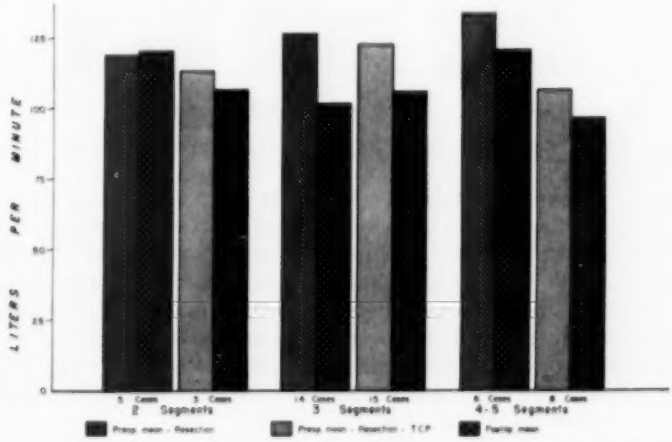

FIG. 1. Maximum breathing capacity: effect of space filling thoracoplasty

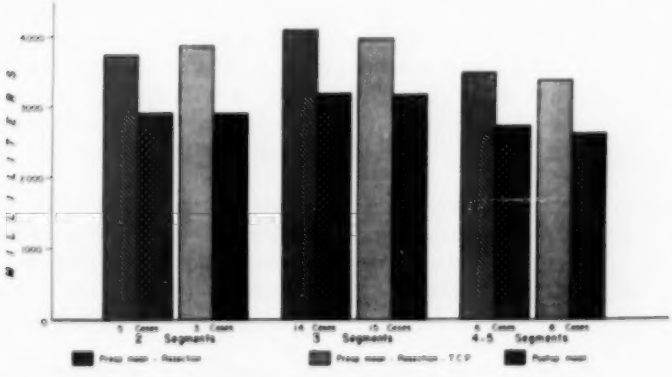

FIG. 2. Vital capacity: effect of space filling thoracoplasty

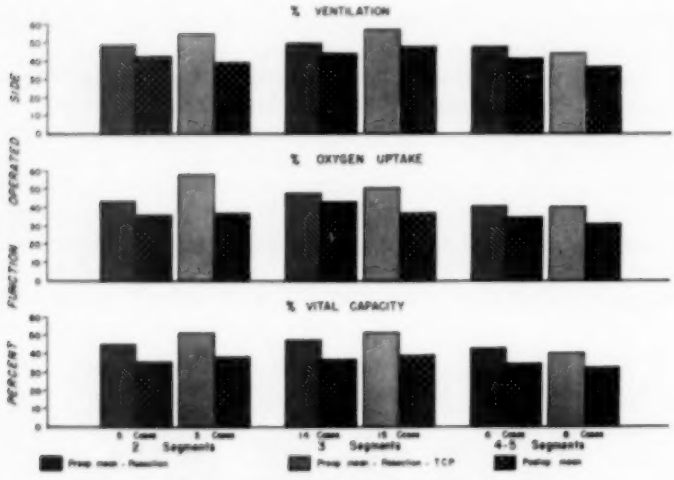

FIG. 3. Bronchospirometry: effect of space-filling thoracoplasty

subgroups in the analysis presented in table 2 in which the purpose was to compare the effect of the removal of increasing numbers of lung segments.

The mean preoperative maximum breathing capacity values varied from 130.1 liters per minute in the one-segment group to 92.4 liters per minute in the ten-segment group. There was great variability of individual values, as indicated by the ranges for each group. The means and ranges did not differ much for the several groups, except possibly for the ten-segment category. The preoperative results, therefore, show a fair degree of uniformity with respect to the ventilatory capacity of the patients before operation.

The maximum breathing capacity results are presented graphically in figure 4. It is apparent in the figure, as in table 2, that there was on the average no change in ventilatory capability after a one- or two-segment resection. In other words, patients who lost function were evenly balanced by patients who gained.

Patients with three to seven segments removed had on the average approximately a 15 per cent reduction of maximum breathing capacity. Here again, some patients gained while most of them lost. Only in the six- to seven- and ten-segment groups were there no patients who showed a gain in maximum breathing capacity, and only in the last group was the average loss slightly greater.

Because of the many factors, some known and others unknown, which enter into the interpretation of pulmonary function tests, biostatistical assistance was sought in evaluation of the data. The results were examined by the methods of variance and covariance analysis. In evaluation of significance, it is assumed that a result which will occur by chance more often than five times in a hundred ($P > 0.05$) is not significant.

By these methods, it was found that the variation of maximum breathing

TABLE 2

PULMONARY FUNCTION DATA ON 74 PATIENTS WITH UNILATERAL RESECTIONS FOR TUBERCULOSIS*

Group	Number of Cases	Ventilatory Tests				Bronchospirometry					
		MBC† l/min. (Mean and Range)		VC‡ ml. (Mean and Range)		Per cent Ventilation Operated Side (Mean and Range)		Per cent VC Operated Side (Mean and Range)		Per cent Oxygen Uptake Operated Side (Mean and Range)	
		Before	Change	Before	Change	Before	Change	Before	Change	Before	Change
1 segment	8	130.1 (97:173)	+1.5 (−9:+13)	4,212 (3,450:5,400)	−569 (−50:−1,400)	45.7 (32:51)	−4.2 (−19:+11)	45.4 (28:52)	−9.4 (−1:−22)	42.9 (30:52)	−2.3 (−20:+8)
2 segments	8	117.0 (77:169)	−1.375 (−42:+48)	3,794 (2,900:4,600)	−869 (−50:−1,250)	50.4 (40:59)	−9.4 (−37:+3)	47.4 (38:61)	−10.6 (−1:−25)	49.1 (26:71)	−12.5 (−49:+6)
3 segments	32	125.5 (77:193)	−15.9 (−48:+27)	3,961 (2,700:5,300)	−820 (−1,750:+200)	54.2 (37:75)	−7.7 (−22:+5)	51.1 (35:76)	−12.3 (0:−34)	49.1 (26:75)	−9.3 (−32:+10)
4 to 5 segments	17	119.4 (70:156)	−14.1 (−51:+16)	3,291 (1,850:4,450)	−641 (−1,500:+50	43.2 (16:59)	−3.7 (−18:+10)	40.1 (13:56)	−7.7 (−25:+18)	38.2 (11:58)	−6.5 (−30:+27)
6 to 7 segments	4	123.5 (67:161)	−16.3 (0:−33)	3,600 (2,750:4,500)	−862 (−550:−1,300)	54.0 (34:81)	−16.0 (−32:+6)	44.3 (30:66)	−10.3 (−35:+15)	41.8 (26:52)	−10.3 (−22:+6)
10 segments	5	92.4 (59:132)	−19.6 (−1:−33)	3,110 (1,900:3,750)	−1,150 (−1,500:+100)	27.8 (10:47)	−27.8 (−10:−47)	24.0 (6:35)	−24.0 (−6:−35)	17.8 (0:31)	−17.8 (0:−31)

* Subgroups *A*, *B*, and *C* of table 1 have been consolidated (*see* text)

† MBC—maximum breathing capacity

‡ VC—vital capacity

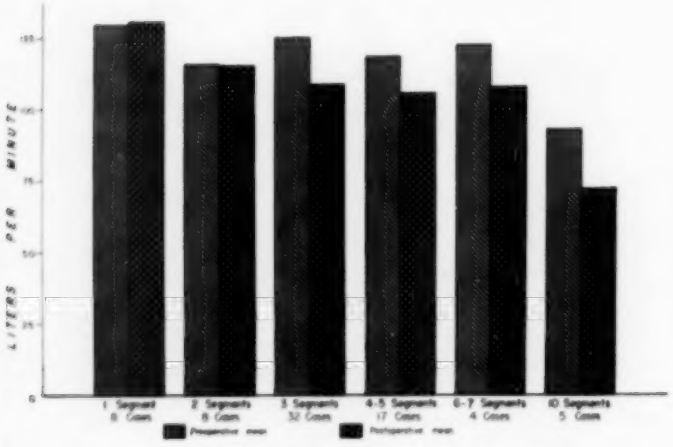

FIG. 4. Maximum breathing capacity—all cases

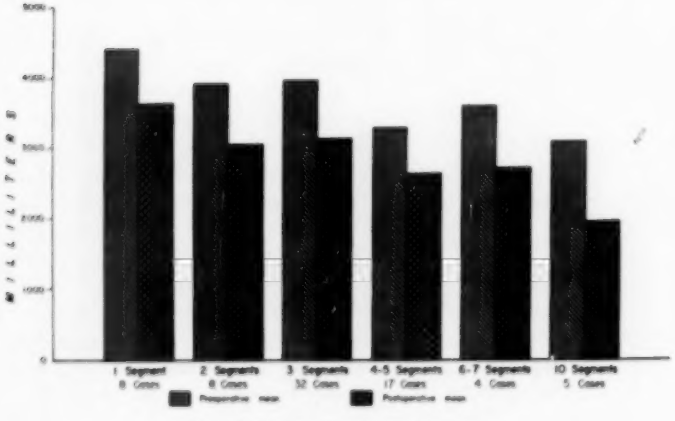

FIG. 5. Vital capacity—all cases

capacity values before surgery did not significantly relate to the number of segments removed or the amount of pre-existing disease. When the losses of pulmonary function following resection were related to the corresponding preoperative values, significant variation of function loss in the different groups occurred ($0.01 < P < 0.05$).

The vital capacity data of table 2 are presented in figure 5. The mean preoperative values, ranging from 4,212 ml. in the one-segment group to 3,110 ml. in the ten-segment group, had a significant relationship to the number of segments removed and correlated with the amount of disease present ($P < 0.01$).

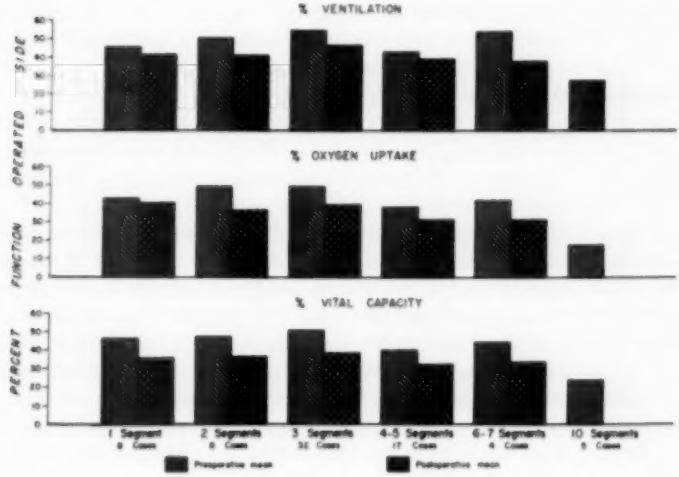

FIG. 6. Bronchospirometry—all cases

Loss of vital capacity was quite similar in the several groups except for being larger in the ten-segment group.

The bronchospirometric data of table 2 are shown in figure 6. The mean values show a slight shift of function to the opposite side in all categories of comparison. The degree of function shift failed to vary with the amount of tissue resected except, of course, after pneumonectomy.

Changes in walking ventilation were minimal and therefore are not tabulated. The mean preoperative value was 16.9 liters per minute and the mean change was an increase of 0.26 liters per minute. Only 7 patients had changes in excess of 5 liters per minute.

DISCUSSION

In evaluating the results of this study, the limitations inherent in the pulmonary function tests must be recognized. The accuracy of such tests in reflecting true alterations of lung function is limited by several factors. The vital capacity and maximum breathing capacity are subject to day-to-day variations of motivation, to errors of measurement, and changes of respiratory muscle capabilities, as well as to alterations of the lung itself. Moreover, no aspect of pulmonary function is entirely uninfluenced by changes elsewhere in the thorax unless the mediastinum happens to be completely rigid.

Some of the factors listed above are of particular pertinence in evaluating pre- and postoperative function. Tuberculous patients, accustomed as they are to a regimen of restricted activity, are likely to be inhibited from maximum effort when asked to perform the violent and exhausting maximum breathing capacity test. By resection, the patient may lose, not only his diseased lung segments, but

also his fear of maximum effort; he may also feel better and be more highly motivated for the post-surgical test. On the other hand, some normal lung tissue is lost even in the best resection, and the healed thoracotomy wound itself may inhibit the more strenuous respiratory gymnastics.

In spite of the presence of these factors which lead to variability in the responses of individual patients, it is apparent that most group averages were definitely altered by surgery. The statistical analysis in general amplified and substantiated the trends suggested by the averages.

The maximum breathing capacity involves the degree of motivation, respiratory muscle power and endurance, resistance to air flow, mobility of the thorax, and only to a moderate degree the volume excursion of the lungs during the maximum breathing capacity test. Since each tidal stroke in the performance of the test involves no more than half the vital capacity (9), one should not expect much, if any, change due to pulmonary factors if only a few segments are removed. This is indeed true for the one- and two-segment groups but is not so for the remainder. This suggests that significant quantities of normal lung were resected in the latter groups in order to include scattered disease foci.

Among factors influencing the vital capacity, many are similar to those affecting the maximum breathing capacity; however, pulmonary distensibility takes the place of resistance as the most important intrapulmonary factor. If other factors were constant, change in vital capacity should be the most sensitive index of the amount of functional lung tissue excised. This did not prove to be the case.

Vital capacity measurements prior to resection indicated a significant correlation with increasing extent of disease. The postoperative changes, however, did not differ significantly among the groups. The degree of loss appeared to be unrelated to the increasing volume resected, suggesting the influence of other more constant factors. Since vital capacity measurement is influenced greatly by chest wall mobility, the similarity of these changes may be a result of altered chest dynamics imposed by the thoracotomy alone. This observation is further amplified by the group with pre-resection thoracoplasty in whom the mean preoperative vital capacity values were lower than those in comparable groups, but who demonstrated less loss following resection. Smith and associates (1) have suggested the importance of the "thoracotomy effect." The present writers believe that such an effect may obscure whatever loss may result from the selective removal of diseased lung segments.

In bronchospirometry one may expect to find a shift of function to the unoperated lung, as was uniformly demonstrated in the present results. Woodruff and associates (2) state that the remaining lung on the operated side almost invariably participates more in ventilation than in oxygen uptake. In the two-, three-, and four to five-segment groups, this relationship was present but only to a slight degree.

SUMMARY

The results of pre- and postoperative ventilatory and bronchospirometric studies performed in 74 patients with unilateral pulmonary resection were

examined. Despite many uncontrollable variables inherent in these function tests, certain inferences appear warranted concerning the influence of resection on pulmonary function.

The preoperative maximum breathing capacity values were not proportionate to the number of segments removed or to the amount of pre-existing disease.

The average postoperative maximum breathing capacity was not changed in the groups in which one and two bronchopulmonary segments were resected; it was reduced approximately 15 per cent in those who had three to seven segments removed; and was reduced by 21 per cent in the pneumonectomy group.

Preoperative mean vital capacity figures reflected the extent of pre-existing disease, but the postoperative losses were remarkably similar in all groups except the pneumonectomy group, and the average loss was approximately 20 per cent. This nearly constant loss may reflect alterations due to thoracotomy alone, which may obscure smaller changes due to removal of diseased lung segments.

Bronchospirometric data showed a slight shift of function to the opposite side in all categories of comparison.

The function changes resulting from resection alone were not significantly influenced by the addition of a post-resection thoracoplasty.

SUMARIO

La Función Pulmonar Antes y Después de la Resección de Segmentos Tuberculosos del Pulmón

Estúdianse aquí los resultados arrojados por los estudios ventiladores y broncospirométricos ejecutados pre- y postoperatoriamente en 74 enfermos sometidos a la resección pulmonar unilateral. A pesar de muchas variables ingobernables que son inherentes en estas pruebas funcionales, parecen justificadas ciertas inferencias acerca del influjo de la resección sobre la función pulmonar.

Los valores preoperatorios de la capacidad máxima respiratoria no guardaron proporción con el número de segmentos resecados o con la magnitud de la enfermedad preexistente.

El promedio postoperatorio de la capacidad respiratoria máxima no varió en los grupos en que se resecaron uno o dos segmentos broncopulmonares. Disminuyó aproximadamente 15 por ciento en aquéllos en que se extirparon de tres a siete segmentos; y 21 por ciento en el grupo de la neumonectomía.

Las cifras preoperatorias de la capacidad vital media reflejaron la extensión de la enfermedad preexistemente, pero las pérdidas postoperatorias mostraron una semejanza notable en todos los grupos excepto el de la neumonectomía, y la pérdida media representó aproximadamente 20 por ciento. Esta pérdida casi constante quizás refleje alteraciones debidas exclusivamente a la toracotomía, que acaso eclipsen alteraciones menores debidas a la extirpación de los segmentos pulmonares enfermos.

Los datos broncospirométricos revelaron una ligera desviación de la función al lado opuesto en todas las clases de comparación.

Las alteraciones funcionales provenientes solamente de la resección no fueron afectadas significativamente por la adición de una toracoplastia post-resección.

RESUME

La fonction pulmonaire avant et après résection de segments pulmonaires tuberculeux

Les résultats pré et postopératoires d'études bronchospirométriques et de la fonction de ventilation pratiquées dans 74 cas de résection pulmonaire unilatérale sont examinés. En dépit de nombreuses variables incontrôlables, inhérentes à ces tests fonctionnels, certaines interférences en relation avec l'influence de la résection sur la fonction pulmonaires paraissent justifiées.

Les valeurs de la capacité respiratoire maxima préopératoire n'étaient pas proportionnelles au nombre de segments réséqués ou à l'étendue des lésions préexistantes.

La capacité respiratoire maxima postopératoire moyenne n'est pas modifiée dans les groupes où la résection comprenait un ou deux segments pulmonaires, elle était réduite d'environ 15% dans les groupes ayant eu de trois à sept segments réséqués et de 21% dans le groupe soumis à la pneumonectomie.

Les chiffres de la capacité vitale moyenne préopératoire reflétaient l'étendue des lésions préopératoires, mais le déficit moyen postopératoire était remarquablement semblable dans tous les groupes, sauf dans celui de la pneumonectomie, et le déficit moyen s'élevait approximativement à 20%. Ce déficit presque constant peut traduire la présence d'altérations imputables à la thoracotomie seule, qui pourraient rendre imperceptibles des modifications plus réduites causées par la résection de segments pulmonaires altérés.

Les données de la bronchospirométrie montraient un faible déplacement de la fonction vers le côté opposé dans toutes les catégories de comparaison.

Les modifications fonctionnelles résultant de la résection seule n'étaient pas influencées de façon significative par l'adjonction d'une thoracoplastie post-résectionnelle.

Acknowledgements

The writers are particularly grateful to Dr. Jane Worcester of the Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, for the statistical analysis of our data.

The ventilatory tests were performed by Miss Marcia E. Jacobs who also prepared the graphs. The services of Mrs. A. E. Hagman in preparation of the manuscript are gratefully acknowledged.

Some of the early data was collected when this laboratory was under the direction of Drs. John J. Cincotti and T. Richard Watson, Jr.

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PULMONARY NITROGEN CLEARANCE AS A CRITERION OF VENTILATORY EFFICIENCY[1, 2, 3]

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INTRODUCTION

Adequate mixing and distribution of tidal ventilation in the lungs are at least as important for the proper aeration of pulmonary blood as the maintenance of a sufficient respiratory volume. Frequently, ventilation may appear to be quite adequate in quantity and yet respiratory gas exchange can be seriously impaired due to the inferior quality of ventilation with regard to its regional distribution and mixing in the alveolar spaces.

The need for a more definite estimate of the quality of ventilation in the clinical evaluation of pulmonary disease has been clearly recognized since the investigations of Cournand and others (1, 2) emphasized the high incidence of ineffective ventilation in many cardiopulmonary ailments. The "index of intrapulmonary mixing" introduced by Darling and associates (3), which represents the nitrogen concentration found in alveolar samples after breathing oxygen for seven minutes in an open system, has been widely adopted for this purpose. Certain limitations of this method are evident, however, in that the measurement does not take into account individual differences in lung volume and in the magnitude of ventilation. The "single breath" method of Fowler (4) employs the nitrogen meter to describe graphically changes in nitrogen concentration in the course of expiration after one breath of oxygen and provides a useful screening procedure to detect the presence of unequal alveolar ventilation. A number of valuable investigations concerning the mechanism of normal and abnormal intrapulmonary mixing have contributed greatly to our knowledge of alveolar ventilation in recent years (5–9). In these comprehensive studies, detailed graphic analyses were made of the dilution rate or mixing rate of an inert gas, either nitrogen or helium, in healthy persons and patients with various forms of pulmonary disease.

A method based on the same principles is described in the present report. The clearance of pulmonary nitrogen while breathing oxygen is used to obtain a reliable measure of ventilatory efficiency by a procedure simple enough to be employed in routine pulmonary function tests.

[1] From the Department of Physiology, Lovelace Foundation for Medical Education and Research, and the Lovelace Clinic, Albuquerque, New Mexico.

[2] Presented before the Medical Session, as part of *Section 5B*, at the annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, May 25, 1955.

[3] This investigation was supported in part by a research grant (PHS-1260C) from the National Heart Institute of the National Institutes of Health, Public Health Service.

METHOD AND PROCEDURE

The arrangement used in the present study is illustrated in figure 1. This is similar to that described by Darling (10) for the determination of the residual volume.

Prior to each test the entire system is flushed out thoroughly with tank oxygen under control with the nitrogen meter. In the first part of the test, the subject, comfortably seated, breathes room air through manifold *A* and the flutter valve, exhaling into the room directly by manifold *B*. The nitrogen concentration during the entire respiratory cycle is recorded continuously via the needle valve *C*. After several minutes, manifold *A* is turned to the oxygen source during normal exhalation and manifold *B* is directed to the spirometer during the following inhalation without disturbing the respiratory pattern of the subject. Thus the air contained in the lungs at the end of normal expiration, plus that in the valve and mouthpiece, is introduced into the system. The nitrogen therein is subsequently collected in the spirometer with the total respiratory volume except for 30 ml. per minute which are diverted from the needle valve to the nitrogen meter. The movements of the spirometer are transmitted electrically to an oscillograph recorder simultaneously with the continuous tracing from the nitrogen meter. The test is terminated when the end-expiratory nitrogen fraction is reduced to 0.01 or less, as indicated on a dial instrument connected in parallel with the recording galvanometer. In healthy subjects this point is reached after three to six minutes on oxygen. In pathologic cases, as long as fifteen minutes may elapse. In such instances the recording of nitrogen elimination is continued after the spirometer has been filled to its capacity (100 liters), and respiratory volume is either extrapolated for the remaining period on the basis of the average measurements obtained on the record previously or collected in a Douglas bag. In the large majority of clinical cases, however, a test of ten minutes' duration is sufficient to obtain the required end point of pulmonary nitrogen clearance.

The *functional residual capacity* (FRC) is then calculated from the volume of nitrogen collected in the spirometer and the difference between the end-expiratory nitrogen fraction at the beginning of the test breathing air and at the end of the test breathing oxygen, as

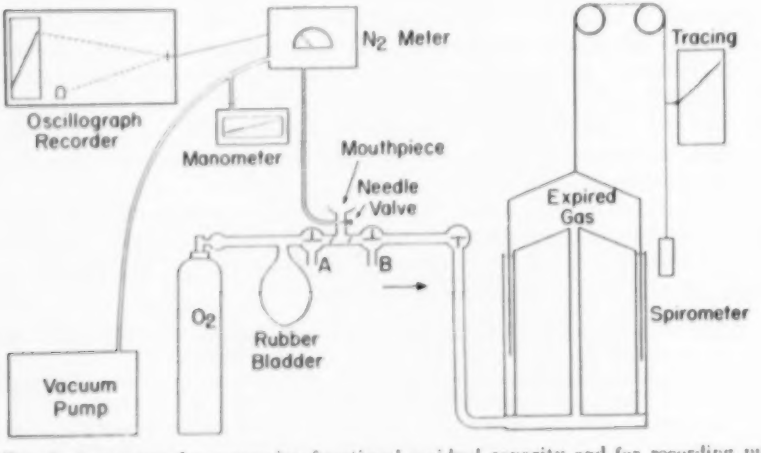

FIG. 1. Apparatus for measuring functional residual capacity and for recording pulmonary nitrogen clearance.

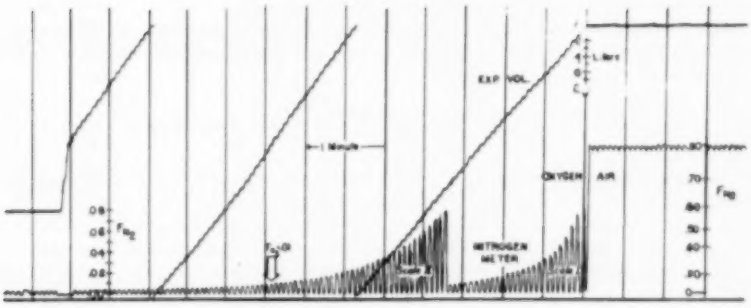

FIG. 2. Pulmonary nitrogen clearance in a normal subject. Read from right to left. In "Scale II" nitrogen meter output is amplified by a factor of 10. The arrow indicates 0.01 fraction of nitrogen in end-expiratory gas.

measured from the record. In this manner no voluntary respiratory maneuvers, such as forced expiration to obtain alveolar samples, are required of the subject. The nitrogen concentration in the spirometer is determined both by chemical analyses (van Slyke) and with the nitrogen meter. Agreement between the two methods was found to be within 0.001 (0.1 volume per cent). Gaseous nitrogen eliminated from the blood and tissues with the exhaled gas was taken into account in the calculation of functional residual capacity by the correction proposed by Cournand and associates (11), based upon the body surface area of the subject and the duration of the test.

The course of *pulmonary nitrogen clearance* as reflected in the expired gas is demonstrated by an original record reproduced in figure 2. The sensitivity of the nitrogen meter is increased by a factor of 10 after the end-expiratory nitrogen level drops below 0.1 fraction. This permits a more precise distinction of pulmonary nitrogen clearance from the nitrogen originating from the blood and tissues which continues to give a measurable deflection for a period of more than an hour. This transition is clearly marked in most instances by a change in slope of a curve drawn through the end-expiratory nitrogen level. It was found empirically that in more than 90 per cent of the cases observed, the end point determined graphically fell within the range of 0.010 and 0.014 fraction of nitrogen in the end-expiratory gas. In those few instances in which the end point of pulmonary nitrogen clearance could not be defined graphically, the 0.01 level was accepted arbitrarily by calibration. While it is understood that the nitrogen concentration at the end of normal expiration does not necessarily represent its mean level in the alveoli—certainly not in advanced emphysema—it is believed that changes in the end-expiratory nitrogen fraction reflect changes in the mean alveolar concentration in true proportion, provided that respiratory rate and tidal volume remain reasonably constant. Nevertheless, it is realized that, in using the end-expiratory nitrogen fraction as a tentative indicator of pulmonary nitrogen clearance, one tends to underestimate rather than overestimate deficiencies in mixing and distribution in the lungs. In view of practical expedience, however, this error is considered acceptable.

Since nitrogen elimination from the lungs is primarily a function of ventilation with oxygen, the total ventilation required to clear the lungs to the chosen end-expiratory nitrogen level (0.010 to 0.014) was used as an over-all measure of ventilatory efficiency. This criterion, referred to in the following as *clearance ventilation*, proved to be more reliable than merely the time or number of breaths recorded, as used in previous studies of this nature.

The clearance ventilation is directly proportional to the lung volume under ventilation, i.e., the FRC, and inversely related to the effectiveness of ventilation. Thus, a person with an unusually large FRC will require a relatively high clearance ventilation even

assuming complete and instantaneous mixing in the lungs. In order to detect the presence and to quantitate the extent of inadequate mixing and uneven distribution, it is necessary to eliminate the lung volume as a variable by relating the clearance ventilation to the FRC of each subject. The value obtained:

$$\frac{\text{total clearance ventilation (liters)}}{\text{FRC (liters)}} = \text{clearance equivalent}^4$$

represents the ventilation which is equivalent to the clearance of one liter of the functional residual capacity to an end-expiratory nitrogen fraction of 0.01.

The *clearance equivalent* provides a measure of ventilatory efficiency most useful in comparing subjects with widely different lung volumes or in evaluating changes in the same subject whose lung volume has changed due to pathologic processes or therapeutic measures. A similar concept was first proposed by Wolfe and Carlson (12) who used the reciprocal of the clearance equivalent as a *pulmonary mixing index* obtained in a closed rebreathing system with oxygen. It must also be considered that, since only that portion of each tidal volume which penetrates into the depth of the lungs becomes effective in the clearing process in the alveoli, both the clearance ventilation and the clearance equivalent may be markedly affected by the relationship *anatomical dead space* (DS) to *tidal volume* (TV). Thus a high DS/TV ratio is associated with a large clearance ventilation, signifying reduced ventilatory efficiency and vice versa.

In certain instances it may be desirable to differentiate between the dead space effect and true intrapulmonary mixing impairment. If the dead space is known or estimated, the alveolar clearance equivalent can be derived as follows:

$$\text{alveolar clearance equivalent} = \frac{\text{clearance ventilation}\left(1 - \frac{\text{DS}}{\text{TV}}\right)}{\text{FRC} - \text{DS}}$$

For clinical purposes, however, the general clearance equivalent is preferable to the alveolar clearance equivalent as the more comprehensive criterion of ventilatory efficiency.

In addition to the determination of the functional residual capacity and the nitrogen clearance ventilation and equivalent described above, the following other measurements of pulmonary function were taken routinely on all control subjects and on as many clinical patients as their condition would permit:

Resting breathing pattern, vital capacity, inspiratory capacity, and expiratory reserve volume from the spirogram on a 9-liter spirometer

Fast vital capacity to obtain 1-, 2- and 3-second fractions of total vital capacity

Maximal breathing capacity for twenty seconds with a low resistance valve and Douglas bag

Respiratory minute volume and gas exchange while walking at 2 m.p.h. on the level treadmill (average oxygen consumption 0.700 liter per minute).

Ventilation reserve for standard exercise:

$$\text{ventilation reserve} = 1 - \frac{\text{exercise ventilation per minute}}{\text{maximal breathing capacity per minute}}$$

Ventilation equivalent for oxygen during exercise

RESULTS

Normal Subjects

The healthy subjects for the control group were chosen with a view to obtaining a wide range of normal variation in age, sex, and body build. It is hoped, in

[4] No correction is made here for the small amount of nitrogen cleared from blood and tissues during the test period.

TABLE 1

MEAN VALUES AND STANDARD DEVIATIONS FOR VENTILATORY FUNCTION STUDIES ON TWENTY-FIVE HEALTHY MALES AND TWELVE HEALTHY FEMALES FROM TWELVE TO FOURTEEN YEARS OF AGE

Control group, 12-64 years

	Volume			Nitrogen Clearance		MBC	Ventilation Reserve 2 m.p.h.
	TC	RV/TC	FRC/TC	Ventilation	Equivalent		
	liters			*liters*	*liters*	*L/min.*	*MBC*
25♂							
M	6.69	0.27	0.52	44.7	13.3	147	0.82
S.D.	1.13	0.06	0.07	9.7	1.3	33	0.05
12♀							
M	4.87	0.27	0.55	37.8	13.9	106	0.82
S.D.	0.59	0.06	0.07	7.7	1.3	24	0.05

TC—total lung capacity; RV—residual volume; FRC—functional residual capacity; MBC—maximum breathing capacity.

time, to derive statistical correlations between standard pulmonary measurements and these variables on a sufficiently large number to predict normal values on this basis.

The mean values and standard deviations (table 1) for total lung capacity and relative subdivisions, for the maximal breathing capacity and ventilation reserve in standard exercise in a group of 25 males and 12 females ranging from twelve to sixty-four years of age were in good agreement with similar data in the literature (13). It will be noted that, while the clearance ventilation showed a relatively large standard deviation primarily due to individual differences in the functional residual capacity, the clearance equivalent with a mean value of 13.3 liters for males and 13.9 liters for females had a standard deviation of only 1.3 liters, or 10 per cent. This is reassuring when it is considered that this value includes not only the biologic variations but also the errors in measurement of the respiratory volume, the determination of the nitrogen clearance point and of the independent computation of the functional residual capacity. This narrow range of variation in ventilatory efficiency may be kept in mind for comparison with the following patients with various forms of pulmonary disease.

Pulmonary Tuberculosis

Of the small number of patients in this group, those designated *Nos. 1* through *6* were suffering from active pulmonary tuberculosis. All of these patients displayed reduced ventilatory efficiency, particularly patients *Nos. 1* and *2* with clearance equivalents above 30 liters. With patients *Nos. 3* through *6*, pneumoperitoneum was induced and the tests were repeated on the succeeding day. In 3 of 4 instances, this procedure resulted in a further loss in ventilatory efficiency, probably associated with the restriction of diaphragmatic movements. Unfortunately, these patients were not available for further study.

TABLE 2

RESULTS OF VENTILATORY FUNCTION TESTS ON ELEVEN PATIENTS WITH PULMONARY TUBERCULOSIS

Number	1 Sex	2 Age	3 TC	4 RV/TC	5 FRC/TC	6 Clearance Ventilation	7 Clearance Equivalent	8 3-Second VC	9 MBC	10 Ventilation Reserve Exercise	Comments
1	M	27	3.67	0.47	0.57	85.5	45.5	0.81	—	—	Active
2	F	47	2.21	0.49	0.67	47.4	32.3	0.84	—	—	Active
3*a*	M	16	4.40	0.33	0.57	43.0	17.6	—	82	0.77	Active
3*b*			4.33	0.23	0.47	39.4	19.5	—	108		Active pneumoperitoneum
4*a*	F	33	2.91	0.23	0.53	41.3	27.0	0.86	—	—	Active
4*b*			3.18	0.31	0.48	30.4	19.9	0.96	—	—	Active pneumoperitoneum
5*a*	M	30	5.72	0.25	0.42	70.2	29.3	0.86	—	—	Active
5*b*			5.48	0.18	0.35	74.4	38.4	0.79	—	—	Active pneumoperitoneum
6*a*	M	29	4.90	0.39	0.60	57.3	19.4	1.00	94	—	Active
6*b*			3.79	0.48	0.68	58.7	22.9	0.98	55	—	Active pneumoperitoneum
7*a*	M	37	5.69	0.22	0.55	35.9	11.5	—	111	0.79	
7*b*			5.88	0.20	0.49	36.1	12.5	—	122	0.80	
8	M	45	5.39	0.40	0.59	38.3	25.0	—	—	—	Old thoracoplasty
9	F	44	2.35	0.46	0.59	43.3	31.3	0.90	43	0.55	Lobectomy 5 years ago
10*a*	M	61	3.22	0.50	0.59	32.0	16.8	1.00	35	—	Pneumonectomy 6 years ago
10*b*			2.59	0.42	0.47	32.7	26.9	1.00	—	—	After pneumoperitoneum
11	M	41	3.64	0.51	0.73	72.7	27.4	0.82	44	—	Left pneumonectomy, scoliosis

TC—total lung capacity; RV—residual volume; FRC—functional residual capacity; VC—vital capacity; 3-second VC means the fraction of VC exhaled forcefully in three seconds; MBC—maximum breathing capacity

Patient *No. 7* had pulmonary tuberculosis which had become arrested after twelve months of treatment, and no abnormalities were found in any of the repeated tests of pulmonary function. The remaining 4 patients with inactive disease had undergone thoracic surgery at least five years before the present observations. All of the patients showed evidence of restrictive impairment and moderate to advanced emphysema in the relative enlargement of the residual volume. The clearance equivalent was unusually high in 3 of the patients treated surgically who had marked mediastinal displacement (in one instance, pronounced scoliosis) while one patient, *No. 10*, had evidently retained satisfactory ventilatory efficiency in the remaining lung after a pneumonectomy six years previously. The clearance equivalent in this patient was considerably increased after pneumoperitoneum, which was then discontinued.

The number of patients observed was too small to warrant any final conclu-

sions. Nevertheless, it may be of some significance that the average of the clearance equivalents in this heterogeneous group of patients with both recent and past histories of pulmonary tuberculosis was higher (24.8 liters) than in any of the other categories of pulmonary disease studied, with the exception of bronchiectasis.

Nontuberculous Pulmonary Disease

The majority of pulmonary function tests (85 tests on 65 patients) were performed on patients who suffered from nontuberculous pulmonary disease. The results have been arranged in table 3 according to the clinical diagnosis in sections designated "Asthma," "Asthma and Emphysema," "Emphysema," "Chronic Bronchitis," and "Bronchiectasis." With very few exceptions it was found that the estimate of ventilatory efficiency based upon the clearance equivalent (column 7) agreed more closely with the subjective and clinical condition of the patient than any other single function test. This was evident, not only in patients under observation for the first time, but also in repeated tests after medication or other therapy such as intermittent positive pressure breathing or after induction of a pneumoperitoneum, as indicated in the last column of the table.

Asthma: In the first section of table 3, of the 12 patients under the primary diagnosis of asthma, 5 were children less than fourteen years of age who were tested before and immediately after intermittent positive pressure breathing treatment combined with bronchodilator aerosol. Although an improvement was found in the three-second vital capacity in most of these children, ventilatory efficiency did not always improve correspondingly. Only one patient with asthma (*No. 12*) showed an extremely high clearance equivalent on first observation. In this case, the patient's asthma of long standing improved remarkably after removal of a thyroid adenoma. The maximal breathing capacity rose from 42 to 100 liters and the clearance equivalent fell from 37 to 21 liters.

Asthma associated with emphysema: The second group in table 3, comprising 18 cases of chronic asthma associated with emphysema, contained no less than 11 patients with a clearance equivalent greater than 25 liters, i.e., nearly double the normal value. The values for the clearance ventilation were correspondingly high. In general, the three-second vital capacity and the maximal breathing capacity were far below normal in these severe cases. Patient *No. 19* provides an interesting example of the reversibility of advanced impairment in some instances in the course of therapy (19*b* and *c*). This is reflected in the sequence of measurements obtained for his relative residual volume and maximal breathing capacity, but particularly in the clearance equivalent which returned to an approximately normal value.

Emphysema: The 25 cases of emphysema with no history of asthma represent the widest range from good to extremely poor ventilatory efficiency of any category in this study. The greatest mixing deficiency was found in a patient whose emphysema was complicated by pulmonary fibrosis (*No. 49*) and in another with silicosis (*No. 40*), both of whom had clearance equivalents close to

TABLE 3

VENTILATORY FUNCTION TESTS ON EIGHTY-FIVE PATIENTS WITH NONTUBERCULOUS PULMONARY DISEASE

Number	1 Sex	2 Age	3 TC	4 RV/TC	5 FRC/TC	6 Clearance Ventilation	7 Clearance Equivalent	8 1-Second VC	9 MBC	10 Ventilation Reserve Exercise	Comments
						Asthma					
1	M	55	6.79	0.33	0.49	48.3	14.5	0.83	—	—	
2	F	69	3.62	0.29	0.54	41.7	20.3	0.77	61	—	
3	M	31	6.93	0.36	0.55	47.4	12.4	—	102	0.87	
4	F	31	4.50	0.52	0.66	71.1	24.0	0.98	58	0.66	
5	M	53	5.50	0.35	0.69	68.7	18.1	0.44	31	—	
6*a*	M	13	3.17	0.12	0.43	23.8	17.7	0.93	—	—	
6*b*			3.37	0.15	0.43	29.8	20.5	0.92	—	—	IPPB
7*a*	F	17	4.31	0.50	0.69	64.3	21.5	0.85	45	—	
7*b*			4.03	0.29	0.54	48.8	22.7	0.90	65	—	IPPB
8*a*	M	9	3.07	0.25	0.44	25.2	18.5	0.92	—	—	
8*b*			3.01	0.23	0.41	23.3	19.0	0.98	—	—	IPPB
9*a*	M	12	3.97	0.17	0.39	27.8	18.1	0.86	—	—	
9*b*			4.24	0.15	0.34	25.6	17.2	0.91	—	—	IPPB
10*a*	M	6	1.97	0.26	0.48	14.7	15.7	1.00	—	—	
10*b*			2.04	0.25	0.38	14.4	18.7	0.99	—	—	IPPB
11*a*	M	6	1.72	0.13	0.51	23.3	26.9	1.00	—	—	
11*b*			1.95	0.18	0.41	16.2	20.2	0.97	—	—	IPPB
11*c*			2.18	0.28	0.50	23.0	21.1	0.94	—	—	IPPB 6 months later
12*a*	M	28	5.00	0.47	0.63	117.7	37.2	—	42	0.46	
12*b*			5.61	0.39	0.62	72.6	20.8	0.87	100	0.79	After removal of thyroid adenoma
						Asthma and Emphysema					
13	M	46	6.76	0.67	0.75	130.1	25.7	0.58	17	0	
14	M	65	6.80	0.51	0.67	163.6	34.9	—	34	0	
15	F	68	4.24	0.42	0.62	52.7	20.2	0.58	34	—	
16	F	36	5.83	0.44	0.67	50.3	12.9	0.66	42	0.62	
17	F	48	4.14	0.47	0.57	49.1	21.0	0.98	47	—	
18	F	48	6.55	0.40	0.60	77.5	18.2	—	68	0.59	
19*a*	M	66	7.15	0.67	0.74	165.9	31.3	0.37	—	—	
19*b*			7.24	0.55	0.72	106.9	20.5	0.33	23	—	IPPB
19*c*			7.86	0.47	0.71	96.6	17.4	0.54	52	—	Meticorten
20*a*	M	67	5.91	0.66	0.81	147.4	31.0	0.42	15	0	
20*b*			5.78	0.59	0.73	134.3	31.8	0.46	15	—	1 week IPPB
21	M	76	6.88	0.59	0.72	138.5	28.1	—	40	—	
22	M	49	7.77	0.44	0.64	87.8	17.7	0.75	121	0.78	
23	M	55	7.61	0.43	0.55	55.1	13.2	0.79	98	0.78	
24	F	50	4.94	0.44	0.64	47.0	14.9	—	—	—	
25	M	68	6.21	0.58	0.69	102.0	23.6	—	28	0	
26	M	57	8.59	0.71	0.82	185.8	26.4	0.39	—	—	
27	F	43	4.90	0.69	0.82	131.0	32.0	—	—	—	
28	M	80	7.11	0.51	0.78	152.0	27.3	0.59	—	—	
29	F	69	4.99	0.50	0.71	89.2	25.3	0.70	41	—	
30	M	53	6.43	0.47	0.61	103.0	26.2	0.54	37	—	

TABLE 3—*Continued*

Number	1 Sex	2 Age	3 TC	4 RV/TC	5 FRC/TC	6 Clearance Ventilation	7 Clearance Equivalent	8 1-Second VC	9 MBC	10 Ventilation Reserve Exercise	Comments
						Emphysema					
31	M	72	7.88	0.39	0.59	57.2	12.2	0.76	67	—	
32	M	52	7.56	0.53	0.69	67.9	13.1	—	90	0.70	
33	F	78	3.97	0.46	0.57	32.0	14.0	0.80	66	0.67	
34	M	70	6.70	0.49	0.61	66.8	16.3	0.84	116	0.71	
35	M	78	5.29	0.34	0.59	57.4	18.3	—	—	—	
36	M	56	5.82	0.54	0.71	68.9	16.6	0.62	—	—	
37	M	72	5.15	0.42	0.62	79.5	24.9	0.63	52	0.35	
38*a*	M	56	7.62	0.57	0.76	117.9	20.3	0.46	32	0.06	
38*b*			7.36	0.56	0.74	123.8	22.7	0.49	33	0.17	10 IPPB treatments
38*c*			6.73	0.57	0.78	110.7	21.2	0.44	21	—	Acute respiratory infection
39	M	64	5.82	0.47	0.65	55.1	14.5	0.74	58	0.18	
40	F	50	3.23	0.69	0.87	130.2	49.9	—	—	—	Silicosis
41	F	53	6.01	0.38	0.63	66.5	17.5	—	76	0.57	
42	M	58	6.62	0.56	0.76	170.5	34.0	—	19	0	
43	M	70	6.77	0.52	0.71	126.6	26.2	0.48	50	0.24	
44	F	34	5.13	0.42	0.59	47.2	15.6	0.96	66	0.51	
45	M	51	7.29	0.39	0.54	65.4	16.7	0.85	146	0.87	
46*a*	M	63	7.46	0.52	0.66	134.0	27.2	—	25	—	
46*b*		64	6.43	0.43	0.63	105.4	26.2	0.45	34	0.22	IPPB
47*a*	M	48	8.41	0.62	0.71	115.5	19.3	0.66	75	0.67	
47*b*			9.12	0.45	0.59	72.5	13.5	0.65	114	0.87	IPPB
48	M	66	7.67	0.49	0.66	80.9	15.9	0.65	68	0.45	
49	F	67	3.21	0.48	0.76	117.6	48.0	0.61	—	—	Fibrosis
50	M	58	6.67	0.58	0.83	227.3	45.2	0.40	—	—	
51	M	59	6.75	0.37	0.58	75.9	19.5	0.59	82	0.59	
						Chronic Bronchitis					
52	M	51	6.18	0.26	0.45	44.1	15.8	0.85	124	0.82	
53	F	40	6.10	0.39	0.59	72.2	20.0	0.94	98	0.62	
54	F	45	4.89	0.31	0.52	48.9	19.3	—	77	0.78	
55*a*	M	11	3.11	0.15	0.39	19.5	16.0	0.97	—	—	
55*b*			2.94	0.12	0.37	19.5	17.7	0.93	—	—	IPPB
56	F	12	2.71	0.17	0.40	17.1	15.9	1.00	—	—	
						Bronchiectasis					
57*a*	F	31	5.28	0.25	0.57	37.5	12.5	—	78	0.74	
57*b*			5.32	0.25	0.56	39.7	13.4	0.89	84	0.77	
58	F	63	4.80	0.52	0.62	64.6	21.6	—	61	0.61	
59*a*	F	29	4.17	0.61	0.79	170.2	51.9	0.57	—	—	

TABLE 3—*Concluded*

Number	1 Sex	2 Age	3 TC	4 RV/TC	5 FRC/TC	6 Clearance Ventilation	7 Clearance Equivalent	8 3-Second VC	9 MBC	10 Ventilation Reserve Exercise	Comments
Bronchiectasis											
59b			4.71	0.48	0.75	108.5	30.8	0.69	—	—	IPPB 1 week
59c			4.78	0.50	0.71	67.5	20.0	0.92	—	—	Pneumoperitoneum initiated
59d			4.75	0.51	0.65	81.8	26.4	0.77	40	—	
60	M	17	5.38	0.32	0.60	49.0	15.1	0.95	84	0.78	
61	F	67	4.13	0.34	0.58	55.6	24.0	—	—	—	
62	F	33	4.90	0.26	0.62	55.9	18.3	0.97	100	0.75	
63	F	23	4.06	0.39	0.58	50.6	21.5	—	43	0.26	
64	F	13	2.35	0.49	0.69	64.6	39.8	0.71	—	—	
65	M	54	6.27	0.27	0.46	55.9	19.6	—	123	0.87	

TC—total lung capacity; RV—residual volume; FRC—functional residual capacity; VC—vital capacity; MBC—maximum breathing capacity; IPPB—intermittent positive pressure breathing.

50 liters. On the other hand, 10 emphysematous patients had normal ventilatory efficiency.

Chronic bronchitis: In 5 cases of chronic bronchitis without signs of emphysema or bronchiectasis, only minor deviations from the predicted ventilatory function were found.

Bronchiectasis: The last 9 patients in table 3 suffered from bronchiectasis of varying degrees, as verified by bronchography. Seven of these were females. In only 3 instances was the ratio residual volume to total capacity unusually high, indicating additional advanced emphysema. On the average, the clearance equivalent in bronchiectasis (24.9 liters) was as high as in the group with pulmonary tuberculosis. A sequence of four tests on the same patient (*No. 59*), with a long history of asthma since childhood with gradual development of bronchiectasis and emphysema, showed the results obtained after one week of regular intermittent positive pressure breathing treatment with medication (*59b*) followed by pneumoperitoneum two weeks later (*59c*). Improvement is most evident in the clearance equivalent but also in the three-second vital capacity and the relative residual volume. A subsequent test after an interval of two months (*59d*) revealed some loss of ventilatory efficiency in the course of a mild recurrence of asthma.

DISCUSSION

The pathology of the various diseases encountered in the present study is generally associated with widespread functional and/or organic changes in the physical properties of the lungs and airways. Hence, it was considered important

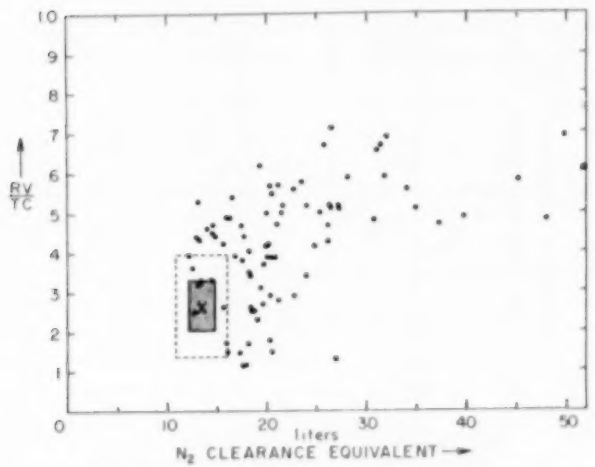

FIG. 3. Eighty-five tests on patients with nontuberculous pulmonary disease plotted with respect to fractional residual volume and nitrogen clearance equivalent.

to ascertain whether a consistent relationship existed between restrictive impairment as reflected in the relative size of the residual volume (RV/TC, column 4) and ventilatory efficiency as measured by the nitrogen clearance test.

The residual volume as a fraction of the total capacity has been plotted in figure 3 against the clearance equivalent for each of the 85 tests listed in table 3. The oblique cross designates the average of all controls, with a hatched rectangle covering one standard deviation, and the larger rectangle two standard deviations, in the normal group. Obviously, there was a trend toward a higher clearance equivalent with increasing relative residual volume. However, no close correlation could be derived therefrom. Moderate and even advanced enlargement of the residual volume was not necessarily associated with any significant impairment of mixing and distribution in the lungs. On the other hand, the 12 patients in the group who had a clearance equivalent of more than 30 liters, indicating extreme ventilatory inefficiency, had RV/TC ratios which ranged from 0.47 to 0.69.

A useful classification of pulmonary emphysema as proposed by Motley (14) has been widely used in recent years. It is based upon the RV/TC ratio as follows:

RV/TC:	0.25-0.35	0.35-0.45	0.45-0.55	0.55-plus
Emphysema:	slight	moderate	advanced	far advanced

In view of the wide variations in ventilatory efficiency found in advanced and extreme emphysema, it appears highly desirable to employ a functional criterion in addition to the volume relationships in the establishment of diagnosis and guidance of treatment. As far as present limited experience permits, ventilatory

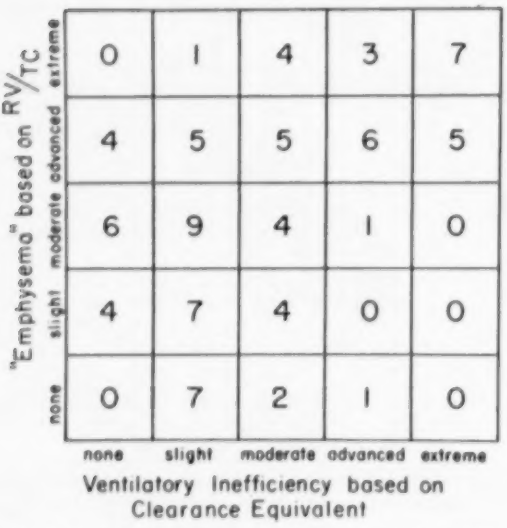

FIG. 4. Evaluation of tests in figure 3 according to volumetric and functional criteria.

inefficiency might be graded in a similar manner:

Clearance equivalent:	15–20	20–25	25–30	30-plus
Ventilatory inefficiency:	slight	moderate	advanced	extreme

In figure 4, the same group of cases has been arranged in a coordinate system with the "volumetric" and "functional" standards. It shows, for instance, that 25 cases classified as advanced "emphysema" according to Motley's scale range fairly evenly from "no ventilatory inefficiency" to extreme impairment. This means that pathologic processes which lead to the restriction of expiratory excursions of the chest and lungs with enlargement of the residual volume are by no means always coincidental with a deterioration of the mixing and distribution function of ventilation. Conversely, ventilatory efficiency may be seriously impaired in the absence of any marked alteration in the total lung volume or its subdivisions.

In conjunction with conventional spirometry, a criterion of ventilatory efficiency as provided by the clearance equivalent with the nitrogen meter is a most valuable tool in the evaluation of the functional aspects of pulmonary disease.

SUMMARY

A method is described for the determination of ventilatory efficiency from the clearance of nitrogen from the lungs while breathing oxygen. The total ventilation required for the clearance of pulmonary nitrogen is dependent upon the lung volume and the efficiency of ventilation with regard to mixing and distribution of gas. The clearance equivalent, a measure of ventilatory efficiency independent

of lung volume, is obtained by dividing the total clearance ventilation of the subject by the functional residual capacity which is measured in the same procedure. The clearance equivalent as measured in 37 normal males and females ranging from twelve to sixty-four years of age showed very small individual variations in healthy persons.

Seventy-six patients with pulmonary tuberculosis and various forms of nontuberculous pulmonary disease were studied with this method in addition to spirometry and other pulmonary function tests. The estimate of ventilatory efficiency based on the clearance equivalent was found to agree more closely with the clinical condition than any other single function test employed. On the average, the ventilatory efficiency of patients with pulmonary tuberculosis was lower than in any other category of pulmonary disease with the exception of bronchiectasis, in which it was of the same order.

The measurement of ventilatory efficiency with the nitrogen meter is proving to be a most valuable aid, not only in evaluating the status and prognosis of a patient, but also in estimating objectively the response to various types of therapy.

SUMARIO

La Eliminación del Nitrógeno Pulmonar como Pauta de la Eficacia Ventiladora

Descríbese un método para determinar la eficacia ventiladora por la eliminación de nitrógeno de los pulmones mientras se respira oxígeno. La ventilación total requerida para la eliminación del nitrógeno pulmonar depende del volumen del pulmón y de la eficacia de la ventilación con respecto a la mezcla y la distribución de gas. El equivalente de eliminación, medida esta de la eficacia ventiladora independiente del volumen pulmonar, se obtiene dividiendo la ventilación eliminadora total del sujeto por la capacidad residual funcional, que se mide en el mismo procedimiento. El equivalente de eliminación, medido en 37 hombres y mujeres normales cuya edad variaba de doce a sesenta y cuatro años, mostró pequeñísimas variaciones individuales en personas sanas.

Setenta y seis enfermos que tenían ya tuberculosis pulmonar u otras formas de neumopatía no tuberculosa fueron estudiados con este método, además de la espirometría y otras pruebas de la función pulmonar. El cálculo de la eficacia ventiladora basado en el equivalente de eliminación resultó más de acuerdo con el estado clínico que ninguna otra prueba funcional empleada. En conjunto, la eficacia ventiladora de los tuberculosos pulmonares fué menor que la de ninguna otra clase de casos pulmonares, con excepción de los de bronquiectasia, en los cuales fué del mismo orden.

La medición de la eficacia ventiladora con el nitrogenómetro va resultando ser una ayuda de los más valioso, no sólo para justipreciar el estado y el pronóstico de un enfermo, sino también para calcular objetivamente la respuesta a varias formas de terapéutica.

RESUME

Clearance de l'azote pulmonaire comme critère de la valeur de la ventilation

Description d'une méthode de détermination de la valeur de la ventilation par la clearance de l'azote pulmonaire pendant l'inhalation d'oxygène. La ventilation totale requise pour la clearance de l'azote pulmonaire est en rapport avec le volume du poumon et la valeur de la ventilation á l'égard du mélange et de la répartition des gaz. L'équivalent de clearance, mesure de la valeur de la ventilation indépendante du volume pulmonaire, s'obtient en divisant la ventilation totale de clearance du sujet par la capacité résiduelle fonctionnelle, qui est mesurée par le même procédé. L'equivalent de clearance obtenu chez 37 sujets sains, hommes et femmes, âgés de douze à soixante-quatre ans, montrait de faibles variations individuelles.

Soixante-seize malades atteints de tuberculose pulmonaire ou de diverses formes d'affections pulmonaires non tuberculeuses ont été étudiés par cette méthode adjointe à la spirométrie et aux autres tests de la fonction pulmonaire. On a découvert que la valeur de la ventilation déterminée par l'équivalent de clearance se repprochait beaucoup plus des conditions cliniques que tout autre test fonctionnel particulier. En moyenne, la valeur de la ventilation dans la tuberculose pulmonaire était plus faible que dans n'importe quelle catégorie d'affection pulmonaire, sauf dans la bronchiectasie où elle était de même ordre.

L'évaluation de l'efficacité de la ventilation par la détermination de l'azote se montre des plus utile, non seulement pour évaleur l'état du malade et le pronostic de la maladie, mais aussi pour évaleur objectivement la réponse aux divers types de traitement.

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INTERMITTENT POSITIVE PRESSURE BREATHING IN PATIENTS WITH PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

Intermittent inspiratory positive pressure breathing (IPPB/I) combined with the nebulization of bronchodilator drugs has been extensively employed in the treatment of chronic pulmonary diseases other than pulmonary tuberculosis (1–5). The objectives of this therapy are to overcome breathing resistance, promote bronchial drainage, relieve bronchospasm, provide a breathing exercise, improve alveolar aeration, and improve pulmonary function. It is natural to exclude active pulmonary tuberculosis from this type of therapy in that rest and collapse of the lung used in the treatment of tuberculosis are directly opposite to the active exercise of positive pressure breathing. Frequently, however, chronic obstructive pulmonary emphysema, fibrosis, bronchitis, bronchospasm, bronchiectasis, accumulation of secretions, edema, poor bronchial drainage, and altered respiratory function are encountered in patients with pulmonary tuberculosis (6). With the increased employment of pulmonary resection in the treatment of pulmonary tuberculosis, it should be helpful both preoperatively and postoperatively to eliminate some of these factors if possible. The use of positive pressure breathing would be desirable providing it had no detrimental effect on the treatment and healing of the tuberculosis.

The object of this study is to determine the effect of intermittent positive pressure breathing in patients with active pulmonary tuberculosis who are being treated with chemotherapy and other supportive measures and to establish criteria for such treatment if indicated. Since the pressures employed (10 to 20 cm. of water) never exceed intrapulmonic pressures developed by coughing (40 to 100 cm. of water) and since pressures in the magnitude of 109 cm. of water are necessary to produce lung damage in dogs (7), it was believed that there was very little hazard to be expected from IPPB/I therapy.

MATERIALS AND METHODS

Twenty-eight patients with far advanced, and one with moderately advanced, active pulmonary tuberculosis of one to twenty-four years' duration receiving chemotherapy (and with evidence of complicating bronchospasm, emphysema, obstruction, and altered respiratory physiology) were selected for IPPB/I treatment. Activity of the disease process was ascertained by the presence of tubercle bacilli. The other factors were determined from the clinical and roentgenographic findings as well as from pulmonary function testing.

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Only inspiratory intermittent positive pressure breathing was employed. A Bennett flow sensitive pressure breathing therapy unit, model TV-3P, equipped with a pressurizing unit and a Halliburton respirator were used. Peak intrapulmonic pressures in the range of 10 to 20 cm. of water were employed. A plastic nebulizer fed by a separate oxygen flow was attached to this apparatus as a source of nebulization of the bronchodilators. It was not necessary to use pure oxygen in the treatment. There was essentially no difference in the effect of the treatment whether air or oxygen was used. Breathing through a mouthpiece at pressures of 15 to 20 cm. of water was well tolerated. A treatment lasting twenty minutes was given three times a day at the beginning and, after a period of three to six weeks, it was reduced to once or twice a day, as necessary according to the patient's response and needs. At the onset of this study, 1 ml. of a bronchodilator solution was used with each treatment. This was prepared by mixing 0.5 ml. of isopropylarterenol hydrochloride (Isuprel®) with an equal quantity of saline. Lately, however, 1 ml. of 1:200 isopropylarterenol hydrochloride has been combined with 9 ml. of oxyethylated tertiary octylphenol-formaldehyde polymer (Alevaire®) and 2 ml. of this mixture has been used per treatment. In special instances not reported in this series, in which secondary infection was evident, antimicrobials were administered by nebulization as well as parenterally. The results of treatment were evaluated subjectively by chest roentgenograms and by pulmonary function tests. A 13.5 liter Collins respirometer was used to measure the vital capacity, timed vital capacity, and maximal breathing capacity. These determinations were routinely employed as objective ventilatory measurements of the response to treatment. These measurements were made in duplicate prior to treatment and were checked periodically during and at the end of a course of therapy.

RESULTS

Clinical data on 29 patients with pulmonary tuberculosis treated with intermittent positive pressure breathing are presented in table 1. Twenty-eight of the patients had active pulmonary tuberculosis with infectious sputum, the character of the disease being fibrocaseous in all instances. The disease was stationary in the chest roentgenograms of all except one (A. A.) who showed evidence of spread of disease within the past year. The duration of IPPB/I administration lasted from one week to ten months. There were no cases of minimal tuberculosis and only one case of moderately advanced, active tuberculosis.

Surgical patients, presented in table 2, were divided into two groups, preoperative and postoperative. There were 15 patients to whom IPPB/I was given preoperatively in preparation for major thoracic surgical procedures. The reasons for giving the intermittent positive pressure breathing and the duration of therapy are listed in table 2. In 6 patients, IPPB/I was started eight days to six months following surgery and was used only in extreme circumstances, in which severe impairment of respiration was evident, to improve ventilatory function and promote bronchial drainage. The IPPB/I was never employed initially in the immediate postoperative period; therefore, it is reasonable to assume that the striking improvement in the clinical condition of these patients was due to the addition of the IPPB/I.

Results of pulmonary function testing in 17 of the patients treated are presented in table 3. Six were medical patients. Pre- and post-treatment measurements were not obtained in all of the 29 patients because of unexpected discharges, surgery, and postoperative circumstances. It can be seen from the data

TABLE 1

CLINICAL DATA ON 29 TUBERCULOUS PATIENTS TREATED WITH INTERMITTENT INSPIRATORY POSITIVE PRESSURE BREATHING (IPPB/I) PLUS BRONCHODILATORS

Patient	Age	Extent of Disease	Duration of Disease	Activity	Duration of Chemotherapy*	Duration of IPPB/I
	years		*years*			
D. G.	46	Far advanced	12	Active	13 months	2 months
S. Y.	36	Far advanced	13	Active	16 months	2 months
W. S.	50	Far advanced	6	Active	2 years	10 months
V. B.	36	Far advanced	8	Active	3 years	4 months
E. C.	50	Far advanced	3	Active	2 years	2 months
L. B.	40	Far advanced	7	Active	3 years	4 months
P. D.	41	Far advanced	5	Active	2 years	3 months
E. D.	37	Moderately advanced	11	Active	2 years	3 months
C. C.	47	Far advanced	8	Active	2 years	4½ months
B. B.	46	Far advanced	19	Active	2 years	2 months
I. R.	48	Far advanced	3	Active	1 year	1 week
J. B.	37	Far advanced	4	Active	3½ years	3 months
A. H.	71	Far advanced	1	Active	6 months	3 weeks
F. L.	59	Far advanced	4	Arrested	1 year	2 months
H. D.	58	Far advanced	2	Active	2 years	1 week
C. L.	51	Far advanced	9	Active	1½ years	16 days
C. W.	52	Far advanced	1	Active	10 months	2 months
W. F.	49	Far advanced	2	Active	2 years	5 days
A. D.	37	Far advanced	24	Active	10 months	2 months
J. E.	30	Far advanced	8	Active	3 years	6 weeks
D. L.	52	Far advanced	4	Active	1 year	3 weeks
L. B.	43	Far advanced	17	Active	3 years	2 months
H. J.	48	Far advanced	10	Active	5 months	2 months
A. A.	58	Far advanced	1	Active	1 year	2 months
A. L.	50	Far advanced	3	Active	4 months	3 months
J. Br.	49	Far advanced	3	Active	3 years	2 months
M. L.	43	Far advanced	15	Active	8 months	2 months
C. H.	63	Far advanced	1	Active	10 months	2 months
E. G.	61	Far advanced	13	Active	3 years	7 weeks

* Prior to the institution of IPPB/I.

in table 3 that there was an average increase in the vital capacity of plus 8.2 per cent, in the maximal breathing capacity of plus 21 per cent, and in the 3-seconds timed vital capacity of plus 4.7 per cent from the pretreatment value.

Patients with pulmonary tuberculosis to whom intermittent positive pressure breathing treatment was administered tolerated the therapy well and had no complaints. In 3 patients (C. L., W. F., and H. D.), therapy was refused after two weeks, one week, and five days, respectively. Apparently, in these patients the intermittent positive pressure breathing was too strenuous and treatment was discontinued. Since the use of IPPB/I therapy was on a voluntary basis, no objections were raised. In all of the patients the tuberculosis was of a stationary nature. Subjective improvement to treatment was difficult to evaluate. In

TABLE 2

INTERMITTENT INSPIRATORY POSITIVE PRESSURE BREATHING (IPPB/I) IN 21 SURGICAL PATIENTS

Patient	Proposed Surgery	Reason for IPPB/I	Duration of IPPB/I
	A. Preoperative		
D. G.	Thoracoplasty	Asthma	2 months
S. Y.	Resection under thoracoplasty	Emphysema	2 months
V. B.	Monaldi drainage followed by thoracoplasty	Low breathing reserve	4 months
H. D.	Resection	Bronchospasm	1 week
C. L.	Resection and 3-rib thoracoplasty	Low breathing reserve	16 days
C. W.	Resection	Bronchospasm	2 months
J. E.	Pneumonectomy	Low breathing reserve	6 weeks
D. L.	Extraperiosteal plombage	Emphysema	3 weeks
L. B.	Resection	Low breathing reserve	2 months
H. J.	Resection	Emphysema	2 months
A. A.	Resection	Bronchospasm	2 months
J. B.	Resection	Bronchospasm	2 months
A. D.	Resection	Bronchospasm	2 months
A. L.	Resection	Emphysema	3 months
J. Br.	Resection	Bronchospasm	2 months
	Surgery Performed		
	B. Postoperative		
W. S.	Segmental resections R.U.L., R.L.L.	Emphysema	10 months
E. C.	3-rib right thoracoplasty	Bronchospasm	2 months
P. D.	7-rib left thoracoplasty	Asthma	3 months
C. C.	Segmental resection L.U.L.	Bronchospasm	3 months
B. B.	Segmental resection R.U.L., R.L.L.	Low breathing reserve	2 months
F. L.	7-rib right thoracoplasty	Emphysema	2 months

general, there was an increased feeling of well-being, decreased coughing, wheezing, and expectoration. For patients in whom bronchospasm was a factor, subjective improvement was very definite.

Following intensive IPPB/I therapy, extending in some patients up to ten months, there was only one instance of any evidence of spread of the tuberculous disease. In this case (J. B.), the patient was subjected to a bronchoscopy, and the spread of disease developed shortly thereafter at a time when he was receiving IPPB/I therapy. The IPPB/I was not discontinued, and regression of the new area of disease occurred; subsequent roentgenograms showed marked improvement in the total disease.

Ten patients had a past history of hemoptysis which occurred three months to three years prior to the institution of IPPB/I. A single small hemoptysis occurred in one patient after two months of daily treatment. The treatment was immediately discontinued and bleeding ceased within forty-eight hours. The

total blood loss was less than 10 ml. It is not certain that this episode of hemoptysis was precipitated by the IPPB/I in that this patient had a history of repeated hemoptyses prior to the institution of such therapy.

In 5 of the patients treated, bronchopleural fistulas were present; treatment was continued in spite of them. In one patient the bronchopleural fistula healed while the patient was receiving positive pressure breathing therapy.

Spontaneous pneumothorax did not occur in any instance where intermittent positive pressure breathing therapy was given. One patient (D. L.) had a history of spontaneous pneumothorax seven years previously. No complication was noted after three weeks of intensive IPPB/I therapy. Several of the patients were receiving pneumoperitoneum simultaneously with the intermittent positive pressure breathing therapy. No untoward effects were noted in this group of patients.

TABLE 3

VENTILATORY MEASUREMENTS BEFORE AND AFTER A COURSE OF INTERMITTENT INSPIRATORY POSITIVE PRESSURE BREATHING (IPPB/I) WITH BRONCHODILATORS IN 17 PATIENTS WITH PULMONARY TUBERCULOSIS

Patient	VC			MBC			TVC	
	Pre	Post	Per Cent of Change	Pre	Post	Per Cent of Change	Pre	Post
	cc.	*cc.*		*L./m*	*L./m*		*per cent*	*per cent*
Surgical								
S. Y.	1,808	1,864	+3.2	63.2	71.1	+12.5	80.0	82.5
V. B.	1,644	2,064	+26.0	29.4	41.1	+40.0	70.0	69.0
P. D.	2,020	2,300	+13.8	43.0	51.1	+18.8	81.0	77.7
J. B.	2,180	2,405	+11.0	46.6	71.1	+53.7	82.0	86.5
C. W.	4,563	5,040	+12.6	56.1	68.5	+22.1	41.0	56.0
A. D.	2,880	2,880	0	56.4	77.5	+37.5	87.0	85.0
J. E.	1,696	1,980	+16.7	56.5	61.3	+8.5	87.0	89.5
H. J.	3,340	3,635	+8.8	69.0	79.6	+15.4	67.5	79.0
A. A.	4,060	4,370	+8.1	117.8	134.5	+14.1	88.0	90.0
A. L.	3,230	3,580	+10.8	73.2	76.6	+2.4	76.6	82.5
J. Br.	3,090	3,060	−0.9	44.0	54.4	+23.6	75.8	76.5
Average	2,774	3,016	+8.5	59.5	71.5	+19.7	76.0	79.5
Medical								
E. D.	2,480	3,345	+35.0	37.8	56.1	+48.5	78.5	79.5
I. R.	2,240	2,485	+10.0	32.0	36.9	+15.3	70.0	73.4
F. L.	2,535	2,470	−3.0	37.2	44.3	+19.0	67.0	78.2
H. D.	3,210	3,655	+13.8	44.3	51.6	+16.5	69.4	83.0
L. B.	2,658	2,570	−3.3	78.1	74.5	−4.8	83.4	90.0
M. L.	2,765	2,600	−5.9	25.4	54.5	+114.5	58.0	65.5
Average	2,648	2,854	+7.8	42.5	53.0	+24.7	70.1	78.2
Average of 17 patients	2,731	2,950	+8.2	53.5	65.0	+21.5	74.3	79.0

VC—vital capacity; MBC—maximal breathing capacity; TVC—timed vital capacity, three seconds per cent of total.

Three of the patients to whom intermittent positive pressure breathing therapy had been given have subsequently died postoperatively from their pulmonary tuberculosis. These deaths were not related to IPPB/I treatment. One death occurred fifty-one days after the IPPB/I had been discontinued. This patient died of respiratory insufficiency postoperatively. The second death occurred as a result of an acute spread of disease to the contralateral lung following a pleuropneumonectomy. In this patient, the IPPB/I had been discontinued five weeks prior to the operation. There was no definite relationship between the spread of the disease and the IPPB/I therapy. The third patient had an advanced degree of pulmonary emphysema with respiratory insufficiency. Following a pulmonary resection, he developed a bronchopleural fistula with severe dyspnea and was virtually maintained constantly on intermittent positive pressure breathing. This patient was a severe respiratory cripple following his surgery and died one year later of respiratory insufficiency. It seemed clear that the positive pressure breathing therapy in this case prolonged the patient's life.

DISCUSSION

Intermittent positive pressure breathing in the treatment of patients with pulmonary tuberculosis was used, not to treat the tuberculosis, but to treat associated conditions which were present. It is believed that this form of therapy has much to offer many tuberculous patients especially those who eventually may need surgical intervention. The judicious use of this adjuvant therapy preoperatively and postoperatively on selected patients may decrease the surgical morbidity and mortality. The improvement in pulmonary function in many borderline cases may be sufficient to enable the patients to successfully withstand an operative procedure and the difficulties encountered in the immediate postoperative period.

Intermittent positive pressure breathing is especially useful in the postoperative period following chest surgery. Theoretically it should help to re-expand the remaining lung after pulmonary resection. Patients following thoracic surgical procedures have impaired ability to cough or breathe deeply because of chest pain; IPPB/I aids in diminishing the effort involved in coughing, elimination of secretions, and improving alveolar aeration. The bronchodilator drugs employed are useful in relieving bronchospasm and encouraging the drainage of secretions. Wetting agents might be useful to liquefy thick tenacious material.

Subsequent to this study, 17 additional tuberculous patients have been treated with IPPB/I. In all, 4,604 IPPB/I treatments have been administered to 46 patients with pulmonary tuberculosis in the past one and one-half years. No difficulties have been encountered in any of these patients. Therapy can be discontinued at any time.

SUMMARY

Twenty-nine patients with active pulmonary tuberculosis receiving chemotherapy and manifesting evidence of bronchospasm, emphysema, and poor pulmonary function were treated with intermittent positive pressure breathing

and aerosols. Generally there was an increased feeling of well-being, decreased cough, wheezing, and expectoration. The therapy was well tolerated and there was no evidence of precipitation of hemoptysis, spread of disease, development of pneumothorax, or interference with the healing process.

An average improvement in the maximal breathing capacity of 21 per cent from the pretreatment value and in the vital capacity of 8.2 per cent was noted.

Intermittent inspiratory positive pressure breathing (IPPB/I) has been used pre- and postoperatively to improve ventilation, relieve bronchospasm, and enhance the elimination of secretions.

To date, 4,604 IPPB/I treatments have been safely administered to 46 patients with pulmonary tuberculosis.

Intermittent positive pressure breathing using pressures of 10 to 20 cm. of water is safe for use when indicated in patients with pulmonary tuberculosis who receive chemotherapy and other supportive measures.

SUMARIO

La Respiración a Presión Positiva Intermitente en la Tuberculosis Pulmonar

A 29 enfermos con tuberculosis pulmonar activa que recibían quimioterapia y manifestaban signos de broncospasmo, enfisema y deficiente función pulmonar se les trató con respiración a presión positiva intermitente y aerosoles. En general, hubo una sensación mayor de euforia y disminución de la tos, del jadeo y de la expectoración. La terapéutica fué bien tolerada, sin observarse signos de precipitación de hemoptisis, difusión de la dolencia, formación de neumotórax u obstrucción del proceso curativo.

Notóse una mejoría media de 21 por ciento en la capacidad respiratoria máxima, comparada con la cifra anterior al tratamiento, y de 8.2 por ciento en la capacidad vital.

La respiración a presión positiva intermitente ha sido usada pre- y postoperatoriamente para mejorar la aireación, aliviar el broncospasmo y aumentar la eliminación de secreciones.

Hasta la fecha, se han administrado sin contratiempo 4,604 tratamientos con respiración a presión positiva intermitente a 46 tuberculosos pulmonares.

La respiración a presión positiva intermitente, usando presiones de 10 a 20 ml. de agua, es inocua para empleo, cuando se halla indicada en tuberculosos pulmonares que reciben la quimioterapia y otras medidas fortalecientes.

RESUME

Respiration avec pression positive intermittente dans la tuberculose pulmonaire

Vingt-neuf malades, atteints de tuberculose pulmonaire en activité, soumis à la chimiothérapie et accusant des signes de brochospasme, d'emphysème et une déficience de la fonction pulmonaire, ont été traités par pression positive intermittente et aérosols. En général, il s'est produit une sensation de bien être croissante, la diminution de la toux, de la respiration sifflante et de l'expectoration. Le traitement a été bien toléré, il n'a pas entraîné d'hémoptysie, extension de la maladie, apparition d'un pneumothorax ou interférence avec le processus de cicatrisation.

Une amélioration moyenne de la capacité respiratoire maxima égale à 21 pour cent, par rapport à ce qu'elle était avant le traitement, et à 8.2 pour cent pour la capacité vitale a été enregistrée.

La respiration sous pression positive intermittente préopératoire et postopératoire a été pratiquée pour améliorer la ventilation, supprimer le bronchospasme et stimuler l'élimination des sécrétions.

A ce jour, 4.604 traitements par respiration sous pression positive intermittente ont été administrés sans incident à 46 malades atteints de tuberculose.

La respiration sous pression positive intermittente, en utilisant des pressions de 10 à 20 ml d'eau, est sans danger quand elle est indiquée chez des patients atteints de tuberculose pulmonaire soumis à la chimiothérapie ou à tout autre traitement d'entretien.

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MORTALITY AND RELAPSE OF UNCOMPLICATED ADVANCED PULMONARY TUBERCULOSIS BEFORE CHEMOTHERPY: 1,504 CONSECUTIVE ADMISSIONS FOLLOWED FOR FIFTEEN TO TWENTY-FIVE YEARS[1, 2]

I. The Relationship of Factors Determined on Admission

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INTRODUCTION

Great advances in the treatment of pulmonary tuberculosis have been made in the past decade. These advances can be measured most effectively against a clear picture of the experience before the advent of effective chemotherapy. Two circumstances have made possible the re-creation of some parts of such a picture: the accumulation of a large reservoir of cases with adequate long-term follow-up at Trudeau Sanatorium; and a new statistical method for the graphic and simultaneous presentation of morbidity and mortality experience with a chronic disease (1). Accordingly, the present report represents a retrospective analysis of the experience at the Trudeau Sanatorium by the use of this statistical method.

MATERIALS AND METHODS

Between January 1, 1930, and December 31, 1939, 2,535 patients were admitted to Trudeau Sanatorium. Of 2,331 with pulmonary tuberculosis, *743* were classified as having minimal lesions, *1,273* as having moderately advanced disease, and *315* as having far advanced pulmonary tuberculosis on admission to the sanatorium. After review of the clinical data and available chest roentgenograms in each case, 137 of those with advanced disease were excluded from further analysis for the reasons outlined in table 1.

There were thus 1,153 patients with moderately advanced and 298 with far advanced *active* pulmonary tuberculosis without *major* tuberculous and nontuberculous complications. In addition, 53 patients, originally classified as having minimal pulmonary tuberculosis, were found upon reclassification to have active, uncomplicated moderately advanced disease (2), thus making 1,206 in all with moderately advanced disease.

The clinical records and all available chest roentgenograms taken before, during, and after residence at Trudeau Sanatorium were reviewed. When the chest roentgenograms were insufficient in number, technically unsatisfactory, or unavailable, the interpretations

[1] From the Trudeau-Saranac Institute, Trudeau, New York.

[2] This study was aided by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] Present address: The Colorado Foundation for Research in Tuberculosis, University of Colorado Medical Center, Denver, Colorado.

TABLE 1

CASES EXCLUDED FROM ANALYSIS AFTER RECLASSIFICATION

Inactive pulmonary tuberculosis:		
Minimal	26	
Moderately advanced	35	61
Active minimal pulmonary tuberculosis (10 with pleural effusion)		14
Pleurisy with effusion only		5
Advanced active pulmonary tuberculosis plus major extrapulmonary tuberculosis complications		
Genitourinary	9	
Bone and joint	8	
Peritonitis	2	
Miliary	2	21
Advanced active pulmonary tuberculosis plus major nontuberculous complications		
Diabetes	13	
Silicosis	5	
Pregnancy	4	
Malignancy	4	
Advanced pulmonary emphysema	3	
Bronchial asthma (severe)	1	
Cardiac decompensation	1	31
Nontuberculous disease only, in retrospect		
Sarcoidosis	1	
Bronchiectasis	1	
Spontaneous pneumothorax	1	
Chronic pulmonary disease, cause undetermined	2	5
Total		137

in the record made by the radiologist were utilized in so far as possible. Details of the clinical course after discharge were obtained from records of readmission to Trudeau Sanatorium; from reports and films obtained from physicians, hospitals, and health departments; from routine yearly follow-up questionnaires to all ex-patients; and, finally, from replies to special questionnaires sent by the writer to all living ex-patients in the study. Treatment either immediately before or after Trudeau Sanatorium residence and continuous with it is considered as part of the original treatment in all cases.

The background features of the patient population are outlined. Most of the patients were young adults with an age range of fifteen to seventy-three and a mean of thirty-one years. There were a few more males (52 per cent) than females. There were only 3 Negroes and 13 Orientals; the vast majority were of northern European ancestry. The socio-economic background was distinctly higher than is usually found in governmentally supported tuberculosis hospitals, particularly those situated in large cities. During the period under study, it was the practice not to admit all patients with very severe disease; for example, those with symptoms of advanced intestinal tuberculosis. Tuberculous complications on admission, not considered grounds for exclusion from study, were relatively infrequent (table 2). Major nontuberculous complications, not considered grounds for exclusion from study, were peptic ulcer in 11 and latent syphilis in 7.

TABLE 2

TUBERCULOUS COMPLICATIONS PRESENT ON ADMISSION

Complication	Moderately Advanced		Far Advanced		All	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
None	883	73.3	130	43.7	1,013	67.4
Pleurisy with effusion	123	10.2	76	25.5	199	13.2
Intestinal	73	6.1	30	10.1	103	6.8
Laryngeal	34	2.8	23	7.7	57	3.8
Endobronchial	30	2.5	7	2.3	37	2.5
Ischio rectal abscess	21	1.7	7	2.3	28	1.9
Otitis media	10	0.8	6	2.0	16	1.1
Cervical adenitis	6	0.5	2	0.7	8	0.5
Empyema	3	0.2	1	0.3	4	0.3
Multiple	23	1.9	16	5.4	39	2.5
Totals	1,206	100.0	298	100.0	1,504	100.0

Descriptive and follow-up data were coded and transferred to an 80-column business machine punch card, using three "mark-sensing" cards for each case.

The results were evaluated in three ways:

(*a*) *Five-year result:* The five-year result was considered "good" if the disease had become clinically controlled with no evidence of cavity and with no tubercle bacilli in the sputum within three years and if relapse had not occurred within the balance of the first five-year period. If a patient was lost through death from nontuberculous causes or if contact with him was lost in less than five years, the case was rated "nonevaluable." Otherwise the result was "poor." Sixty-seven moderately advanced and 8 far advanced cases were "nonevaluable," leaving 1,429 cases for analysis by this method.

(*b*) *The twenty-year tuberculosis morbidity*[6] *and mortality* (corrected for differences in duration of observation): Because it includes all available data, this method was considered more reliable than the five-year results. Patients were regarded as "sick" during a year if they were under treatment for active tuberculosis for six months or more.

(*c*) *Primary relapse rates:* Patients were considered at risk of relapse after achieving clinical control of disease. Relapse is defined as any unfavorable roentgenographic and/or bacteriologic events leading to active treatment. The primary relapse rate is defined as the incidence of first relapses corrected by life table for differences in the year of onset after arrest.

The statistical analyses were carried out by mechanical sorting and tabulation of the punch cards. A master table was made in search of hidden correlations.

[6] Morbidity is defined for the purposes of this paper as active tuberculosis under treatment, whether it was the original illness or a relapse.

TABLE 3

ROENTGENOGRAPHIC PROGRESSION OF DISEASE DURING SANATORIUM RESIDENCE

Progression	Moderately Advanced		Far Advanced		All	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
None	919	76.2	159	53.7	1,078	71.9
Mild	39	3.2	7	2.3	46	3.0
Severe	161	13.4	56	18.8	217	14.4
Multiple	87	7.2	76	25.2	163	10.7
Totals	1,206	100.0	298	100.0	1,504	100.0

Differences in proportions were tested for statistical significance by the standard error and chi-square methods. Differences in life tables were tested at the five-, ten-, and fifteen-year levels. A difference which might have arisen from chance alone in no more than 2 per cent of cases was considered significant (*S*).[4] All differences which failed to meet this criterion were rated as nonsignificant (*NS*)[4] even though in many instances they may have been indicative of possible or even likely interdependence of the developments being tested.

RESULTS

Progression of disease at the sanatorium: Mild, severe, or multiple progressions of disease were noted in 426 of the 1,504 patients (table 3). Progression of disease is defined as the appearance of new roentgenographic shadows or the definite intensification of pre-existing ones; these were classified as "mild" when the increase in shadowing was slight or minimal. The monthly or yearly incidence of progressions at the sanatorium is not known because duration of stay ranged from four weeks to more than twenty years, but this sort of information has been determined elsewhere (3). Thirty-seven patients died of progressive tuberculosis at the sanatorium. This is not a true reflection of the severity of disease treated because it was sanatorium policy to attempt to transfer patients to other sanatoriums or to their homes if death appeared inevitable.

Tuberculosis morbidity and mortality: The cumulative tuberculosis mortality is shown in the diagonally lined space labeled "dead tuberculosis" beneath the lower curve in figure 1 (moderately advanced) and figure 2 (far advanced). The stippled space labeled "sick" in figure 1 represents the proportion of living contacted ex-patients who were being treated for active tuberculosis during six or more months of each year after admission. For obvious reasons, this was 100 per cent in the first year unless death occurred in less than six months. The clear space labeled "well" represents the proportion of patients well and able to work in each year of observation. At the top of these graphs is recorded the cumulative proportion of patients lost to the study through death from nontuberculous causes and loss of contact.

In subsequent figures showing tuberculosis morbidity and mortality, proportions of "well," "sick," and "dead tuberculosis" were computed by eliminating data on patients

[4] *S* = statistically significant: A difference which might have arisen from chance alone in no more than 2 per cent of cases. All differences which failed to meet this criterion were rated as nonsignificant (*NS*) even though, in many instances, they may have been indicative of possible or even likely interdependence of the developments being tested.

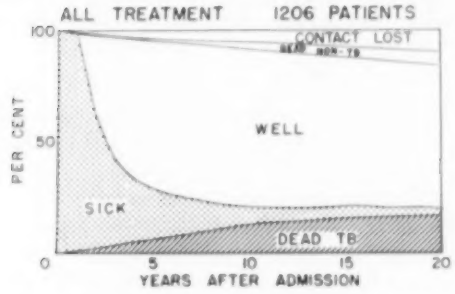


FIG. 1. Twenty-year morbidity and mortality experience of 1,206 consecutive patients with active *moderately* advanced pulmonary tuberculosis without major complications.

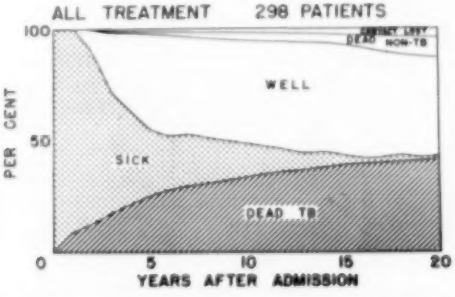


FIG. 2. Twenty-year morbidity and mortality experience of 298 consecutive patients with active *far* advanced pulmonary tuberculosis without major complications.

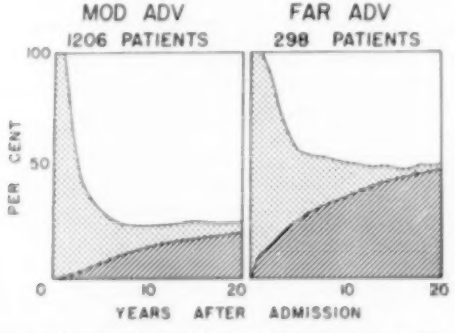


FIG. 3. Twenty-year tuberculosis morbidity and mortality experience of 1,504 patients with advanced pulmonary tuberculosis; by extent of disease on admission. Data on loss of contact or death from nontuberculous causes are excluded.

lost through death from nontuberculous causes or loss of contact *after* the loss had occurred. The same marking is used where possible, viz: "well" (*clear*), "sick" (*stippled*), and "dead tuberculosis" (*diagonally lined*).

The 1953–1954 status of the 1,504 patients is shown in table 4. Twenty-seven per cent were dead (21 per cent from tuberculosis), 3 per cent were sick with tuberculosis, 9 per cent were lost from observation, and the balance (61 per cent) were apparently well.

Extent of disease: Tuberculosis mortality was greater (*S*) with far advanced (figure 2) than with moderately advanced (figure 1) disease. Morbidity, on the other hand, had a greater tendency to persist over the years in the moderately advanced than in the far advanced group. These differences are shown more clearly in figure 3, showing both groups of cases simultaneously after excluding the nonpertinent data on losses. At least in part because of a difference in the patient population, these results are more favorable than those recently reported from a state hospital (4, 5).

TABLE 4

1953–1954 Status of All 1,504 Patients with Advanced Pulmonary Tuberculosis and No Major Complications, Admitted to Trudeau Sanatorium 1930–1939

Condition	Moderately Advanced		Far advanced		All	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Well	789	65.5	140	47.0	929	61.8
Under treatment for active tuberculosis	37	3.0	8	2.7	45	3.0
Dead, tuberculosis	195	16.3	120	40.2	315	20.8
Dead, nontuberculous causes	70	5.7	19	6.4	89	5.9
Sick, then contact lost	24	2.0	1	0.3	25	1.8
Well, then contact lost	91	7.5	10	3.4	101	6.7
Totals	1,206	100.0	298	100.0	1,504	100.0

TABLE 5

Five-Year Results by Density of Roentgenographic Shadows and Size of Largest Cavity on Admission

Density of Roentgenographic Shadows	Cavity														
	No Cavity			0.5–1.0 Cm.			1.5–2.0 Cm.			2.5 Cm. +			All Cases		
	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent
Light	144	60	41.7	84	41	48.8	47	21	44.7	45	21	46.7	320	143	44.7
Medium	143	69	48.3	112	51	45.5	118	43	36.4	96	33	34.4	469	196	41.8
Heavy	66	24	36.4	56	33	58.9	97	48	49.5	130	78	60.0	349	183	52.4
Undetermined	101	40	39.6	59	28	47.5	61	28	45.9	70	37	52.9	291	133	45.7
All	454	193	42.5	311	153	49.2	323	140	43.3	341	169	49.6	1,429	655	45.8

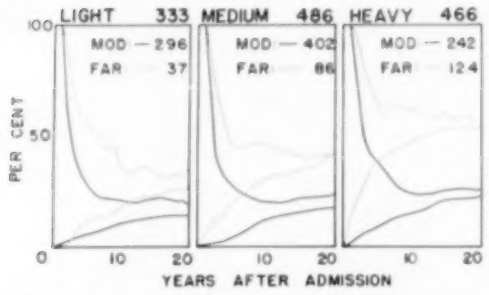


FIG. 4. Twenty-year tuberculosis morbidity and mortality experience: by density of roentgenographic shadows and extent of disease. (Two hundred and nineteen patients were excluded because a satisfactory film taken at the beginning of treatment was not available.)

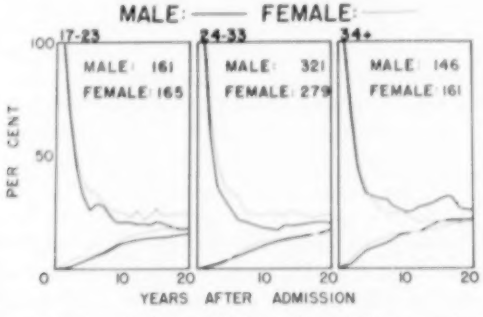


FIG. 5. Twenty-year tuberculosis morbidity and mortality experience with *moderately* advanced pulmonary tuberculosis: by age and sex of patients.

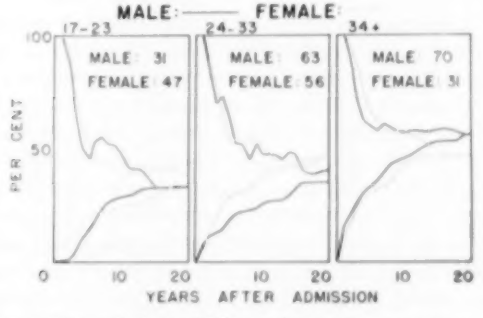


FIG. 6. Twenty-year tuberculosis morbidity and mortality experience with *far* advanced pulmonary tuberculosis: by age and sex of patients.

TABLE 6

FIVE-YEAR RESULTS BY AGE, SEX, AND EXTENT OF DISEASE ON ADMISSION

	15-23			24-33			34+			All Ages		
	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent
Moderately Advanced												
Male	152	63	41.4	301	115	38.2	140	62	44.3	593	240	40.5
Female	161	76	47.2	266	115	43.2	119	53	44.5	546	244	44.7
Total	313	139	44.4	567	230	40.6	259	115	44.4	1,139	484	42.5
Far Advanced												
Male	29	18	62.1	61	38	62.3	69	47	68.1	159	103	64.8
Female	46	22	47.8	55	30	54.5	30	16	53.3	131	68	51.9
Total	75	40	53.3	116	68	58.6	99	63	63.6	290	171	59.0
All Cases												
Male	181	81	44.8	362	153	42.3	209	109	52.2	752	343	45.6
Female	207	98	47.3	321	145	45.2	149	69	46.3	677	312	46.1
Total	388	179	46.1	683	298	43.6	358	178	49.7	1,429	655	45.8

The extent of disease was also measured by cavity size and the density of the roentgenographic shadows. This factor is considered as much a measure of the inflammatory nature of the lesion as it is a measure of extent. The five-year results did not seem to vary with the density of shadows (table 5). On the other hand, the morbidity and mortality experience with far advanced disease did vary (*S*) with the density of roentgenographic shadows (figure 4). The greater the density of the shadows the poorer the result. This factor had previously been found to be an important prognostic sign in patients receiving pneumothorax (6).

Age and sex: By five-year results, males with far advanced pulmonary tuberculosis had a much less (*S*) favorable course than males with moderately advanced disease, a difference that was not nearly as striking (*NS*) in females (table 6). Using the age groups fifteen to twenty-three, twenty-four to thirty-three, and thirty-four-plus and again dividing cases into those of moderately advanced and those of far advanced disease, there were no other important age or sex differences. Using the twenty-year morbidity and mortality experience (figures 5 and 6), the results in far advanced disease were slightly (*NS*) less favorable with advancing age for both sexes, especially males. There were no differences in the results by age and sex in the group with moderately advanced disease.

Year of admission: Judging both from the five-year results (table 7) and the

TABLE 7

FIVE-YEAR RESULTS BY EXTENT OF DISEASE AND YEAR OF ADMISSION

Year of Admission	Moderately Advanced			Far Advanced			All		
	Total	Poor	Per Cent	Total	Poor	Per Cent	Total	Poor	Per Cent
1930–1931	306	127	41.5	51	30	58.8	357	157	44.0
1932–1933	227	102	44.9	67	35	52.2	294	137	46.6
1934–1935	216	87	40.3	75	53	70.1	291	140	48.1
1936–1937	211	85	40.3	54	28	51.9	265	113	42.6
1938–1939	179	83	46.4	43	25	58.1	222	108	48.6
All	1,139	484	42.5	290	171	59.0	1,429	655	45.8

morbidity and mortality experience (figure 7), there was no particular change in the effectiveness of treatment during the ten-year period. There was, on the other hand, a considerable reduction in the number of admissions per year and no particular change in the proportion of those with far advanced disease.

Age of disease: Patients who failed to react to tuberculin and/or had a negative chest roentgenogram within eighteen months before admission were classified as having "newly acquired" disease. Patients admitted because of reactivation of disease seen on a chest roentgenogram two or more years before admission were classified as having "old" disease. The age of disease in the balance (81 per cent) was "undetermined." Results in the undetermined were somewhat less favorable than in the known group. In addition, 26 per cent of the "old" cases were far advanced while this was true of only 7 per cent of the "newly acquired" cases. For these reasons the very slight (*NS*) difference in favor of newly acquired disease in figure 8 is not considered reliable.

Age of disease was also estimated from the duration and nature of symptoms and the character of the major roentgenographic shadows in serial films taken before and at admission and classified as "new," "mixed," and "old." Particular attention was paid the position of the root and mediastinal shadows and other evidence of pulmonary contraction.

Using this method of estimating age of disease and subdividing cases into moderately and far advanced disease, there was no difference in moderately advanced but a considerable difference (*S*) in far advanced disease (figure 9). The experience with 32 patients with "old" disease was more than twice as unfavorable as the experience with 138 with "new" disease; 67 with "mixed" disease fell nicely between these two extremes.

Cavity size and location: There was surprisingly little correlation (*NS*) between the presence and size of the largest cavity by five-year results subdivided by National Tuberculosis Association classification or twenty-year morbidity and mortality (figure 10). Four hundred and seventy-two patients with no cavity on admission showed a 22 per cent twenty-year tuberculous mortality while, at the other extreme, 349 with cavities of 2.5 cm. or more experienced a 28 per cent tuberculous mortality; the mortality tended to occur earlier and morbidity was

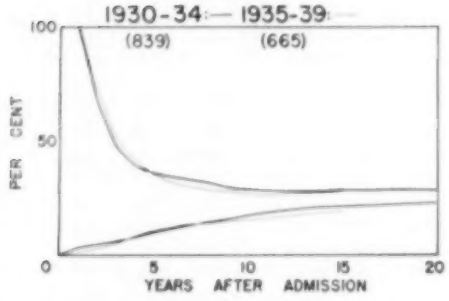


FIG. 7. Twenty-year tuberculosis morbidity and mortality experience: by year of admission.

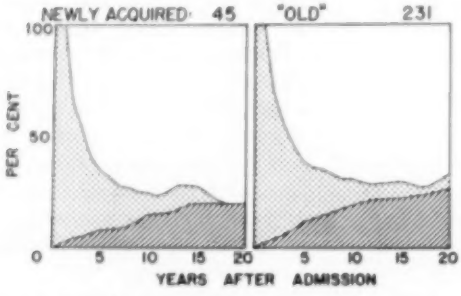


FIG. 8. Twenty-year tuberculosis morbidity and mortality experience: by known age of disease on admission. (One thousand one hundred and fifty-nine patients were excluded because age of disease was undetermined.)

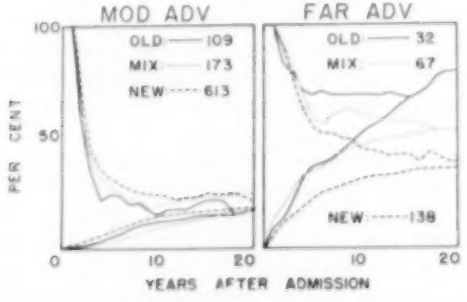


FIG. 9. Twenty-year tuberculosis morbidity and mortality experience: by extent and *estimated* age of disease.

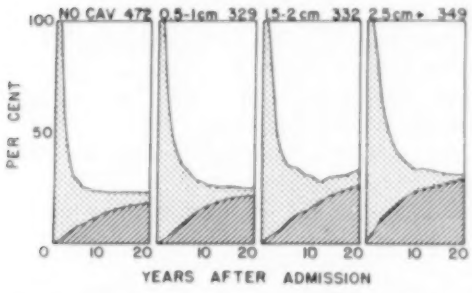
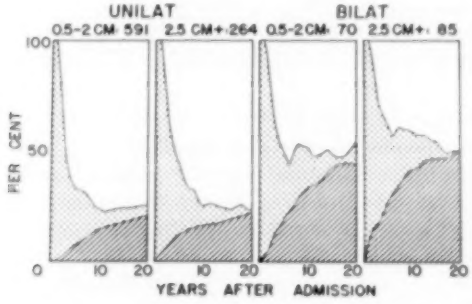


FIG. 10. Twenty-year tuberculosis morbidity and mortality experience: by presence and size of largest cavity seen on admission.



., FIG. 11. Twenty-year tuberculosis morbidity and mortality experience: by size of unilateral and bilateral cavity on admission.

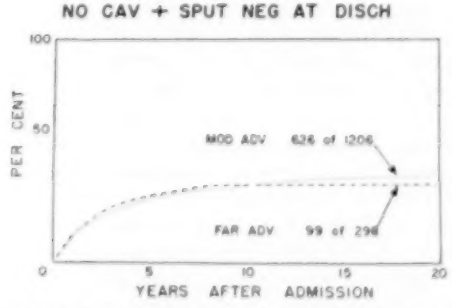


FIG. 12. Primary relapse rates of advanced pulmonary tuberculosis by extent of disease on admission.

greater in the latter group. Those with 0.5 to 1 cm. and 1.5 to 2 cm. cavities fell between these two categories.

This observation confirms the recent findings of Alling, Lincoln, and Bosworth who studied the total diameter of all cavities in far advanced disease (5). McMahon found that cavity closure at discharge was related to size on admission, but had no long-term data on this point (7).

There was no demonstrable relationship between the location of the cavity within the lung and the results attained.

The twenty-year morbidity and mortality of tuberculosis in relation to the presence on admission of unilateral and bilateral cavity is presented in figure 11. The patients are further subdivided into those in whom the largest cavity was 2 cm. in diameter or more and those in whom the largest cavity was less than 2 cm. The big difference with respect to cavity proved to be the question whether cavitation was *unilateral* or *bilateral*. The twenty-year tuberculous mortality was 20 and 50 per cent, respectively. Only minor differences were introduced by the *size* of these cavities. The present results are more favorable than those previously reported in 1933 and 1942, in which there was only about 25 per cent five-year survival of patients with unilateral and less than 10 per cent five-year survival of those with bilateral cavity on admission to the hospital (7, 8).

Location of disease: In general, there was a tendency for the results to be more favorable the more the disease was localized to one lung. There was no demonstrable relationship between location of cavity and results. There was however, a consistent difference (*NS*) in the behavior of disease predominantly in the right versus the left lung. The disease in the left lung apparently behaved more favorably. This is the subject of a separate report (9).

Other factors: Doctors and nurses as a group fared about the same as those not occupationally exposed to the disease.

Acid-fast bacilli were demonstrated in the sputum of 96 per cent of the patients by microscopy. Sputum cultures were performed only in very selected cases and only after 1936. Analysis of cases by the bacteriologic findings on admission was therefore considered noncontributory.

The presence of the tuberculous complications of laryngeal, intestinal, and endobronchial tuberculosis, corrected for differences in extent of pulmonary disease, was associated with relatively unfavorable five-year results (*S*).

Relapse after arrest of disease: Arrest of disease was actually observed in 626 of 1,206 (52 per cent) of those with moderately advanced and in 99 of 298 (33 per cent) of those with far advanced disease (figure 12). Primary relapse occurred in approximately 28 per cent at some time during the ensuing twenty years. The incidence and timing of relapse was *not* materially influenced by the extent of disease on admission, confirming recent reports (4, 5).

Fifty-seven per cent of primary relapses had occurred within two years after discharge, 72 per cent after three years, and 86 per cent had occurred within five years. Sporadic primary relapse continued to occur up to twenty-two years after discharge. It may be argued that some of these very late relapses represented exogenous rather than endogenous reinfections (10).

COMMENT

The prognosis of advanced pulmonary tuberculosis in a selected patient population was more favorable than has previously been reported (11–14). This is probably attributable to the favorable socio-economic background and to the tendency to avoid the admission of patients with the major complications of pulmonary tuberculosis.

The fact that cavity presence and size had no demonstrable influence on prognosis was surprising. The selection of treatment may have played a part in this unexpected finding (15).

The incidence and timing of relapse was surprisingly unaffected by the original extent of disease, once it had become arrested. The incidence of relapse of minimal disease after achievement of arrest was an almost identical 27 per cent (2).

It now appears clear that the behavior of pulmonary tuberculosis during the first five years after institution of treatment creates a fairly reliable picture of what to expect in the future. Whether this will continue to be true of the disease since the advent of chemotherapy remains to be seen.

To judge from the experience of others, the rather limited influence of age and sex in this series may be due to the limited numbers of patients more than forty years old.

SUMMARY

One thousand five hundred and four relatively selected patients were admitted to Trudeau Sanatorium between 1930 and 1939 with advanced active pulmonary tuberculosis without major tuberculous and nontuberculous complications. The annual status for the next fifteen to twenty-five years was determined with loss of contact in less than 10 per cent of the whole group.

After twenty years the cumulative tuberculosis mortality was approximately 20 per cent for moderately advanced and 50 per cent for far advanced disease.

Approximately one-half of the patients with moderately advanced and one-third of those with far advanced disease achieved arrest of disease before discharge from the sanatorium. Primary relapse occurred in approximately 28 per cent of both the moderately and far advanced groups during the ensuing twenty years, mostly within the first five years after discharge.

Morbidity and mortality rates were apparently influenced by the extent of the lesions, the increasing age in males, the apparent age of disease and density of roentgenographic shadows in far advanced disease, and by the presence of bilateral versus unilateral cavity.

Tuberculosis morbidity and mortality rates were apparently unaffected by age in females, the year of admission during 1930–1939, and the location and size of cavity.

SUMARIO

La Mortalidad y las Recidivas en la Tuberculosis Pulmonar Avanzada sin Complicaciones Antes de la Quimioterapia: 1504 Ingresos Consecutivos Mantenidos en Observación 15–25 Años. I. La Relación de los Factores Determinados al Ingreso

Mil quinientos cuatro enfermos algo seleccionados fueron recibidos en el Sanatorio Trudeau entre 1930 y 1939, mostrando tuberculosis pulmonar activa avanzada sin mayores

complicaciones tuberculosas o no tuberculosas. Durante los quince a veinticinco años siguientes se determinó anualmente el estado de los enfermos perdiéndose de vista a menos de 10 por ciento.

Al cabo de veinte años, la mortalidad tuberculosa acumulativa era aproximadamente de 20 por ciento para la enfermedad moderadamente avanzada y de 50 por ciento para la muy avanzada.

Toscamente, la mitad de los que tenían enfermedad moderadamente avanzada y la tercera parte de los que la tenían muy avanzada lograron estacionamiento de la dolencia antes del alta. Hubo recidivación primaria aproximadamente en 28 por ciento de ambos grupos durante los veinte años transcurridos, principalmente dentro de los primeros cinco años consecutivos al alta.

La morbidad y la mortalidad se vieron al parecer afectadas adversamente por la extensión de las lesiones, el avance de la edad en los varones, la edad aparente de la enfermedad y la densidad de las sombras radiográficas en la enfermedad muy avanzada, y por la presencia de cavernas bilaterales en vez de unilaterales.

La morbidad y la mortalidad tuberculosas no fueron al parecer afectadas por la edad en las mujeres, el año de ingreso durante 1930–1939 y la localización y el tamaño de la caverna.

RESUME

Mortalité et Rechute dans la Tuberculose pulmonaire avancée non compliquée, avant la Chimiothérapie: 1504 Admissions consécutives suivies pendant 15 à 25 Ans. I. Rapport entre les facteurs déterminés à l'admission

Il a été admis au Sanatorium Trudeau, entre 1930 et 1939, 1504 malades relativement sélectionnés. Ces sujets présentaient une tuberculose pulmonaire active étendue, sans complications tuberculeuses ou non tuberculeuses majeures. L'état annuel a été déterminé pour les quinze à vingt-cinq années suivantes; la perte de contact avec les patients était inférieure à 10 pour cent.

Au bout de vingt ans, le taux cumulatif de mortalité était approximativement de 20 pour cent pour les cas moyennement étendus et 50 pour cent pour les cas très étendus.

En gros, l'arrêt de la maladie a été observé avant la sortie de l'hôpital chez un tiers de ceux présentant une tuberculose moyennement étendue et un tiers des cas dont l'affection était très avancée. Dans les deux groupes, la rechute initiale s'est produite dans approximativement 28 pour cent des cas au cours des vingt années suivantes; la plupart dans les cinq premières années suivant la sortie de l'établissement de cure.

La morbidité et la mortalité semblaient influencées de façon adverse par l'étendue des lésions, l'augmentation de l'âge chez l'homme, la durée apparente de la maladie et la densité des ombres radiologiques dans les cas très étendus, ainsi que par la présence de cavernes bilatérales par opposition aux lésions cavitaires unilatérales.

La morbidité et la mortalité par tuberculose ne paraissaient pas influencées par l'âge chez la femme, l'année de l'admission au cours de la période 1930–1939, ni par le siège et les dimensions de la caverne.

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MORTALITY AND RELAPSE OF UNCOMPLICATED ADVANCED PULMONARY TUBERCULOSIS BEFORE CHEMOTHERAPY: 1,504 CONSECUTIVE ADMISSIONS FOLLOWED FOR FIFTEEN TO TWENTY-FIVE YEARS[1, 2]

II. The Relationship of Type of Treatment and Status on Discharge

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INTRODUCTION

One thousand five hundred and four patients with active advanced pulmonary tuberculosis without major tuberculous and nontuberculous complications were admitted to Trudeau Sanatorium between 1930–1939 and, in more than 90 per cent of the group, the patients were followed to death or to 1953–1954 (1). A retrospective analysis of these cases was concerned with factors determinable at the beginning of treatment (1). The present report is a further analysis of the same patients by events which occurred during sanatorium residence and by the treatment used.

A description of the materials and methods is presented in the first report.

OBSERVATIONS

Results by type of collapse used: An attempt was made to determine the relative effectiveness of the various forms of treatment being used in 1930–1939. A patient was classified as having received pneumothorax when refills were continued for six months or more. A patient was classified as having received phrenic nerve interruption only if hemidiaphragmatic paralysis was obtained. Patients having thoracoplasty often had had pneumothorax and/or phrenic nerve interruption first. Because of the small numbers, all patients who had thoracoplasty were so classified whether they had had pneumothorax and/or phrenic nerve interruption before or not.

As measured by "five-year results" (*see* the first paper of this series for definition (1)) in 1,425[4] of 1,429 patients, the best (*NS*)[5] treatment for moderately advanced disease was "no collapse" while the best (*S*)[5] results in far advanced

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[2] This study was aided by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

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[4] Four of the 1,429 patients available for study of five-year results had some form of treatment other than pneumothorax, phrenic nerve interruption, thoracoplasty, or no collapse.

[5] *S* = statistically significant: A difference which might have arisen from chance alone in no more than 2 per cent of cases. All differences which failed to meet this criterion were rated as nonsignificant (*NS*) even though, in many instances, they may have been indicative of possible or even likely interdependence of the developments being tested.

TABLE 1

FIVE-YEAR RESULTS BY USE OF COLLAPSE IN EFFECT AT DISCHARGE AND EXTENT OF DISEASE ON ADMISSION

Collapse Used	Moderately Advanced			Far Advanced			All		
	Total	Poor Results		Total	Poor Results		Total	Poor Results	
		Number	Per Cent		Number	Per Cent		Number	Per Cent
None	612	244	39.9	85	60	70.6	697	304	43.6
Pneumothorax	366	164	44.8	125	67	53.6	491	231	47.0
Phrenic nerve interruption	96	43	44.8	28	20	71.4	124	63	50.8
Pneumothorax plus phrenic nerve interruption	31	17	54.8	10	7	70.0	41	24	58.5
Thoracoplasty	33	16	48.5	39	17	43.6	72	33	45.8
All	1,138	484	42.5	287	171	59.6	1,425	655	46.0

(Four "other" collapses)

disease were obtained with thoracoplasty. Pneumothorax was second best in the far advanced group and apparently more effective (*NS*) than phrenic nerve interruption and no collapse.

Using the twenty-year morbidity[6] and mortality experience (figure 1), however, there was little or no difference, except a greater loss of time in the thoracoplasty patients (*NS*).

These results doubtless reflect the hesitation to accept thoracoplasty on the part of both patients and physicians characteristic of those "early days." Moreover, there was some additional delay in returning to work occasioned by the then rather drastic surgery. On the other hand, the results with thoracoplasty are especially good when it is considered that there was a much higher proportion of far advanced disease in this group than in the other groups.

In addition, the thoracoplasty candidates usually represented *failures* of rest and reversible collapse treatments.

The thoracoplasty mortality was either surgical or a result of primary failure to achieve control of disease rather than late relapse. This may be seen in figure 2. In the figure are recorded all patients admitted with moderately advanced disease who had achieved control of their disease at the time of discharge from treatment, as measured by cavity and bacteriologic findings.

There has been no tuberculous mortality in 16 thoracoplasty patients (*S*) (this was true of 43 with far advanced disease as well) whose disease had been brought under control thereby. This was not the case with 323 with no collapse, 229 with pneumothorax, and 58 with phrenic nerve interruption whose disease was apparently just as well controlled at discharge. The comparability of these observations is not adversely influenced by the fact that thoracoplasty was often delayed until after obvious failure of other forms of treatment.

[6] Morbidity is defined for the purposes of this paper as active tuberculosis under treatment, whether it was the original illness or a relapse.

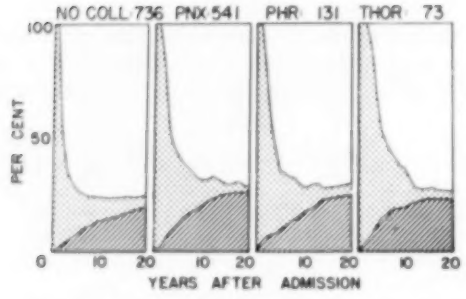

FIG. 1. Twenty-year tuberculosis morbidity and mortality experience of 1,481 consecutive patients with advanced pulmonary tuberculosis with major complications: by four types of treatment used. (Twenty-three patients were excluded because "other" treatment was used.)

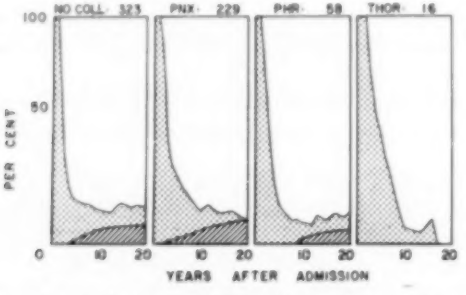

FIG. 2. Twenty-year tuberculosis morbidity and mortality experience of 626 consecutive patients with *moderately* advanced pulmonary tuberculosis, discharged with no cavity or tubercle bacilli in the sputum: by type of treatment used.

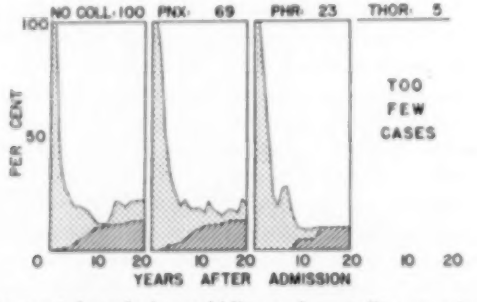

FIG. 3. Twenty-year tuberculosis morbidity and mortality experience of 197 *selected* patients with *moderately* advanced pulmonary tuberculosis with one cavity 1 to 2 cm. in diameter in one lung, minimal disease in the other, and tubercle bacilli in the sputum on admission, and no cavity or bacilli in the sputum at discharge: by type of treatment used.

Similar data is presented in figure 3 on a very select group of patients meeting criteria set up to permit an even more reliable comparison. All had moderately advanced disease, a 1 to 2 cm. cavity in one lung, minimal disease in the other, tubercle bacilli in the sputum on admission to the hospital, and control of disease by cavity and sputum findings on discharge. The findings duplicate those noted in figures 1 and 2, namely, that little difference exists between the various treatments except thoracoplasty, of which there were only 5 cases.

Results by use of pneumothorax: Pneumothorax proved to be less effective than no collapse (*S*) when no cavity was present. Pneumothorax was equally effective when small (0.5 to 2.0 cm.) cavities were present and was more effective when large (2.5 cm. or more) cavities were present (figure 4). Some doubt is raised about the validity of this observation because patients who received no collapse for the first two to twelve months would often receive pneumothorax later because of progression of disease or failure to achieve control of the disease.

An effort was then made to determine the relationship of the timing of the initiation of pneumothorax to the results obtained (figure 5).

In the first place, the timing of pneumothorax (divided into those initiated within the first six weeks of treatment and those initiated later) was related to the presence and size of cavity on admission (*S*): the larger the cavity, the earlier pneumothorax was initiated. Second, the twenty-year morbidity and mortality experience was not influenced by this factor.

In figure 5 it is also indicated that pneumothorax results as measured by the twenty-year morbidity and mortality experience were not influenced by the presence or *size* of cavity, divided between those smaller and those larger than 2 cm. in diameter.

The twenty-year morbidity and mortality experience with 110 patients who were found to have empyema following pneumothorax therapy may be seen in figure 6. The five-year mortality was 30 rising to 50 per cent at twenty years, confirming a previous observation made by a less comprehensive method (4).

Primary relapse rates by type of treatment: All patients who had achieved control of disease by the time of discharge from the hospital, as measured by absence of cavity and negative bacteriologic findings, were considered at risk of relapse.

Relapse is defined as any unfavorable roentgenographic and/or bacteriologic event leading to active treatment. The primary relapse rate is defined as the incidence of first relapses corrected by life table for differences in the year of onset after arrest. In figure 7, confined to 626 such patients with moderately advanced disease on admission, and previously studied in figure 2, by far the most favorable experience (*S*) was again observed with thoracoplasty: there was only a 5 per cent relapse rate in twenty years. There was little difference between the other three forms of treatment except that, with phrenic nerve interruption, relapse was prone to occur earlier (*NS*) and more often (*NS*) than with pneumothorax or no collapse.

The experience with *far advanced* disease was entirely comparable with that seen with moderately advanced disease but was based upon too few cases to justify recording the data. The twenty-year primary relapse rate in 43 such patients treated with thoracoplasty was again 5 per cent.

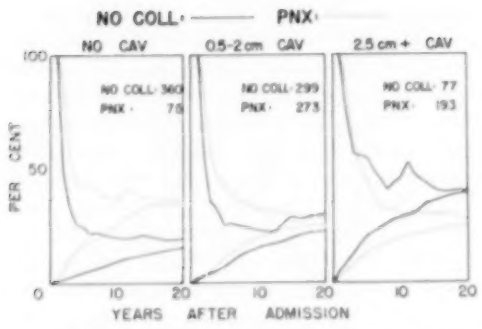

FIG. 4. Twenty-year tuberculosis morbidity and mortality experience of 1,277 consecutive patients with advanced pulmonary tuberculosis: by presence and size of cavity on admission and use of pneumothorax or no collapse.

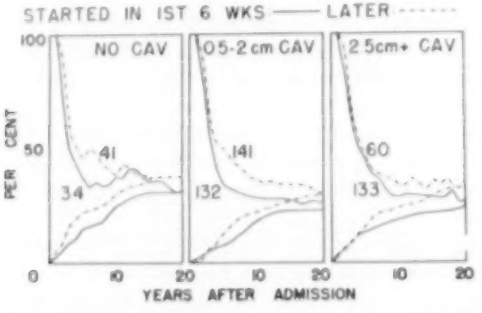

FIG. 5. Twenty-year tuberculosis morbidity and mortality experience of 541 consecutive patients with advanced pulmonary tuberculosis treated with pneumothorax: by the timing of the initiation of pneumothorax and size of cavity present.

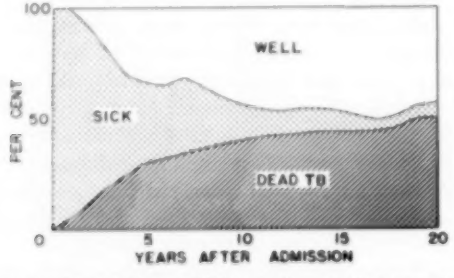

FIG. 6. Twenty-year tuberculosis morbidity and mortality experience of 110 patients with advanced pulmonary tuberculosis who developed tuberculous empyema complicating artificial pneumothorax.

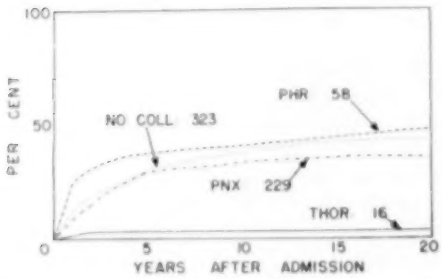

FIG. 7. Primary relapse rates of *moderately* advanced pulmonary tuberculosis: 626 patients with no cavity or tubercle bacilli in the sputum at discharge: by type of treatment used.

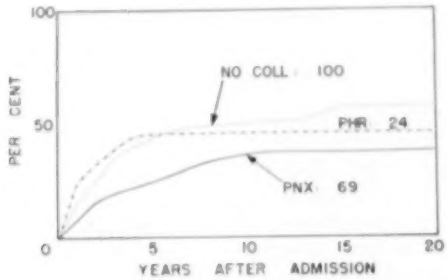

FIG. 8. Primary relapse rates of 197 selected patients with *moderately* advanced pulmonary tuberculosis with one cavity 1 to 2 cm. in diameter in one lung, minimal disease in the other lung and tubercle bacilli in the sputum on admission, and no cavity or tubercle bacilli in the sputum on discharge: by type of treatment used.

In figure 8 the same very select group of patients with moderately advanced disease described in figure 3 were at risk of relapse. There were only 5 with thoracoplasty, none of whom had relapse. The results were approximately the same as those shown in figure 7 except that those with no collapse were the least favorable (*NS*).

Results by status at discharge: Five-year results by the National Tuberculosis Association classification (Diagnostic Standards, 1950 edition) at discharge are shown in table 2. The results were more favorable in those patients discharged "apparently arrested" or "arrested" than in those discharged as "quiescent" or "active" (*S*). Slight differences within these two groups, however, were not significant.

In table 3, the presence or absence of cavity and the bacteriologic findings at the time of discharge from the hospital are measured by the five-year results. The presence of cavity and tubercle bacilli in the sputum were of about equal prognostic importance and the best results were being observed in patients with no cavity *and* no demonstrable tubercle bacilli in the sputum. In addition, there

was nothing to choose between the two types of criteria evaluated in tables 2 and 3.

In patients discharged under favorable circumstances by either of these criteria (tables 2 and 3), the original extent of the lesion (whether moderately or far advanced) *had no influence* on five-year results or primary relapse rates. When discharged with unfavorable findings, however, experience with far advanced disease was much less favorable (*S*).

Six hundred and ninety-seven of 736 patients who did not receive collapse treatment spent at least six months at the sanatorium, were alive on discharge, and had chest films which were available for review. The over-all change in

TABLE 2

FIVE YEAR RESULTS BY EXTENT OF DISEASE ON ADMISSION AND BY THE NATIONAL TUBERCULOSIS ASSOCIATION CLASSIFICATION AT DISCHARGE

NTA Classification at Discharge	Moderately Advanced			Far Advanced			All		
	Total	Poor Results		Total	Poor Results		Total	Poor Results	
		Number	Per Cent		Number	Per Cent		Number	Per Cent
"Quiescent" or "active"	907	398	43.9	243	151	62.1	1,150	549	47.7
"Arrested" or "apparently arrested"	188	62	33.0	23	7	30.4	211	69	32.7
All	1,095	460	42.0	266	158	59.4	1,361	618	45.4

(Sixty-eight patients were excluded because of death at sanatorium or a stay too short to permit classification.)

TABLE 3

FIVE YEAR RESULTS BY CAVITY AND BACTERIOLOGIC FINDINGS AT DISCHARGE AND EXTENT OF DISEASE ON ADMISSION

Discharge Findings		Moderately Advanced			Far Advanced			All		
Cavity Presence	Bacteriology	Total	Poor Results		Total	Poor Results		Total	Poor Results	
			Number	Per Cent		Number	Per Cent		Number	Per Cent
No	Negative	698	235	33.7	114	40	35.1	812	275	33.9
	Positive	209	98	46.9	45	21	46.7	254	119	46.9
	All	907	333	36.7	159	61	38.4	1,066	394	37.0
Yes	Negative	84	53	63.1	9	7	77.8	93	60	64.5
	Positive	98	70	71.4	96	88	91.7	194	158	81.4
	All	182	123	67.6	105	95	90.5	287	218	76.0
All	Negative	782	288	36.8	123	47	38.2	905	335	37.0
	Positive	307	168	54.7	141	109	77.3	448	277	61.8
	All	1,089	456	41.9	264	156	59.1	1,353	612	45.2

(Seventy-six patients were excluded because of death at sanatorium or inadequate data.)

TABLE 4

FIVE-YEAR RESULTS BY ROENTGENOGRAPHIC CHANGES IN FIRST SIX TO TWELVE MONTHS: CASES WITH NO COLLAPSE ONLY

Clearing of Shadows	Pulmonary Contraction											
	Yes			No			Undetermined			All		
	Total	Poor Results		Total	Poor Results		Total	Poor Results		Total	Poor Results	
		Number	Per Cent		Number	Per Cent		Number	Per Cent		Number	Per Cent
Marked	88	24	27.3	125	37	29.6	24	6	25.0	237	67	28.3
Slight	63	32	50.8	134	64	47.8	22	10	45.5	219	106	48.4
No change	19	8	42.1	51	27	52.9	10	3	30.0	80	38	47.5
Worse	12	9	75.0	45	39	86.7	10	10	100.0	67	58	86.6
Undetermined	5	0	0.0	4	2	50.0	85	33	38.8	94	35	37.2
All	187	73	39.0	359	169	47.1	151	62	41.1	697	304	43.6

(Thirty-six patients were excluded because of death at sanatorium or inadequate data.)

serial roentgenograms for the first six to twelve months was classified as "marked clearing," "slight clearing," "no change," "worse," and "undetermined." The pulmonary status of these same patients was also classified by the presence or absence of pulmonary contraction, i.e., a demonstrable shrinkage of aerated lung in the involved area during treatment. This latter factor was not determined in 151 patients because adequate films permitting a review of six to twelve months of treatment were not available or because evaluation of this factor was obscured by pleural changes and the like. Patients receiving collapse were excluded from this study not only because contraction was thus artificially produced in most such cases, but also because the changes in roentgenographic shadows were often obscured thereby. The findings in table 4 were almost entirely those obtained on discharge of these patients.

In table 4 it is evident that five-year results were better when "marked clearing" occurred than when there was only "slight clearing" or "no change" (*S*). On the other hand, there was no demonstrable relationship between five-year results and the occurrence of visible pulmonary contraction. Among those with no clearing i.e., "no change," those with pulmonary contraction fared somewhat better than those with no contraction (*NS*).

Results by amount of bed rest maintained: Attempts to correlate retrospectively the amount and kind of rest taken with the results obtained in pulmonary tuberculosis have been unsatisfactory at best (2) and even misleading (3).

In the present study, the patients who did not receive collapse were studied in various groups by the extent of the original lesion, on the one hand, *and* the amount of modified bed rest, the duration of sanatorium residence, and time away from full employment, on the other. A group of patients with approximately an equal amount of moderately advanced disease with one cavity (*see* figures 3 and 8) were studied separately. The consistent finding in all of these

subgroups was that the *more* rest taken according to all three definitions, the *poorer* the five-year results (*8*).

COMMENT

The comparison in retrospect of patients treated in different ways is notoriously unreliable, principally because of the differing reasons for the selection of the treatment for each patient. It was common practice during the nineteen-thirties at Trudeau Sanatorium to observe patients on rest for several weeks or months before trying a pneumothorax or phrenic nerve interruption, the latter usually first. Primary thoracoplasty was preceded by pneumothorax, phrenic nerve interruption, or attempts thereat in 52 of the 73 patients so treated. On the other hand, in those days patients had to be in a rather favorable general condition before being acceptable for major surgery. Under these circumstances the record made by those patients receiving thoracoplasty is still quite impressive.

On the other hand, a great many patients were given pneumothorax within a few weeks after diagnosis, often before admission to Trudeau Sanatorium. Contrary to a common belief, early pneumothorax did *not* appear to be any less effective (or more dangerous) than when it was delayed for six weeks or more. This may be due, however, to the inclusion in the early pneumothorax group of many patients who would have done perfectly well on rest alone.

Studying many of the same patients, cavity size was previously found to be related to results at the end of the first year, at abandonment of pneumothorax, and three years later (*4*). The present study used different criteria to measure results and divided cases into two groups, with cavity larger and smaller than 2 cm., in contrast to three groups (0.5–3.0, 3.5–6.0, and more than 6.5 cm. in diameter) in the earlier study. The major difference was that the determination of cavity size was made on admission in the present study and immediately before induction in the earlier one.

It should be re-emphasized that the inability to demonstrate a relationship between the results and the amount of rest taken does not mean that more rest is not beneficial and less rest is beneficial. There is little doubt that the findings here reflect the clinical condition of the patient and the good judgment of the physician in the individual case rather than the ineffectiveness of rest. The findings indicate, moreover, that there are no statistical techniques to permit the introduction of individual differences which were evident to the patient's physician at the time but not recordable in a chart or visible upon review of the films. In short, it is very probable that more rest was usually prescribed (and taken) by the patient with the less favorable over-all clinical situation.

SUMMARY

One thousand five hundred and four consecutive patients with advanced active pulmonary tuberculosis with no major tuberculous and nontuberculous complications were admitted to Trudeau Sanatorium in 1930–1939 and followed for fifteen to twenty-five years with loss of contact in less than 10 per cent.

As measured both by tuberculosis mortality and relapse, and before the intro-

duction of effective chemotherapy, thoracoplasty has stood the test of time far better than pneumothorax, phrenic nerve interruption, or no collapse.

Relapse was apt to occur earlier following achievement of control of disease with phrenic nerve interruption than with pneumothorax or no collapse.

Late pneumothorax results were not related to the presence or size of cavity nor to whether it was initiated within six weeks of the beginning of hospital treatment or later.

Pneumothorax was more effective in far advanced disease than phrenic nerve interruption or no collapse. The three methods were of approximately equal effectiveness in moderately advanced disease.

The results in patients who did not receive collapse varied with the degree of clearing but not with the degree of pulmonary contraction seen during the first six to twelve months of treatment.

SUMARIO

La Mortalidad y las Recidivas en la Tuberculosis Pulmonar Avanzada sin Complicaciones Antes de la Quimioterapia; 1504 Ingresos Consecutivos Mantenidos en Observación 15–25 Años. 2. La Relación entre la Clase de Tratamiento y el Estado al Dar el Alta

Mil quinientos cuatro enfermos consecutivos con tuberculosis pulmonar activa avanzada, pero sin mayores complicaciones tuberculosas o no tuberculosas, fueron recibidos en el Sanatorio Trudeau en 1930–1939 y mantenidos en observación durante quince a veinticinco años, perdiéndose de vista a menos de 10 por ciento.

Apreciada a la luz tanto de la mortalidad tuberculosa como de las recidivas, y antes de la introducción de la quimioterapia eficaz, la toracoplastia ha resistido la prueba de los años mejor que el neumotórax, la avulsión del frénico o la falta de colapso.

Las recidivas mostraron propensión a presentarse más tempranamente a continuación del dominio de la enfermedad con la avulsión del frénico que con el neumotórax o a falta del colapso.

Los resultados del neumotórax tardío no se relacionaron con la presencia de cavernas o el tamaño de éstas ni con su iniciación en término de seis semanas del principio de la enfermedad o más tarde.

El neumotórax resultó más eficaz en la enfermedad muy avanzada que la avulsión del frénico o que la falta de colapso. En la enfermedad moderadamente avanzada, los tres métodos mostraron una eficacia aproximadamente igual.

Los resultados en los enfermos que no recibieron colapso variaron de acuerdo con la magnitud del despejo, pero no con el grado de la contracción pulmonar observada durante los primeros seis a doce meses de tratamiento.

RESUME

Mortalité et Rechute dans la Tuberculose pulmonaire avancée non compliquée, avant la Chimiothérapie—1504 Admissions consécutives suivies pendant 15 à 25 ans. II. Rapport entre le Type de Traitement et L'État de L'Affection à la Fin de la Cure

Une série consécutive de mille cinq cent quatre malades atteints de tuberculose pulmonaire active très étendue, sans complications tuberculeuses ou non tuberculeuses majeures, ont été admis au Sanatorium Trudeau de 1930 à 1939. Ces cas ont été suivis pendant quinze à vingt-cinq ans; le contact a été perdu avec 10 pour cent des malades.

Par rapport au taux de mortalité et de rechute, et avant l'introduction d'une chimiothérapie efficace, la thoracoplastie a beaucoup plus favorablement soutenu l'épreuve du temps que le pneumothorax, la paralysie du phrénique ou l'absence de collapsus.

La rechute était susceptible de se produire plus tôt après la réalisation du contrôle de l'affection par la paralysie du phrénique, que par le pneumothorax ou l'absence de collapsus.

Les résultats éloignés du pneumothorax ne dépendaient ni de la présence ou de la dimension de la caverne, ni s'il était instauré dans les six premières semaines du traitement ou plus tard.

Le pneumothorax était plus efficace dans les cas plus avancés que la paralysie du phrénique ou l'absence de collapsus. Les trois méthodes possédaient une efficacité approximativement égale dans les cas moyennement étendus.

Les résultats obtenus chez les patients n'ayant pas été soumis au collapsus variaient selon le degré d'éclaircissement du poumon, mais non avec celui de la contraction pulmonaire observée durant les six à douze mois du traitement.

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ON THE PROGNOSIS OF CHILDHOOD TUBERCULOSIS[1, 2, 3]

An Eighteen-Year Follow-Up Report

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INTRODUCTION

In a thesis published in 1934 and entitled "Étude Clinicobactériologique sur la Possibilité de Déceler la Présence de Bacilles Tuberculeux chez l'Enfant par la Méthode du Lavage de l'Estomac" (1), the results were reported of investigations in 349 children. The study was subsequently extended to comprise 434 children up to fifteen years old. The final results were published in 1935 (2). These children had received sanatorium care for suspected or verified active pulmonary tuberculosis. In all cases roentgenographic examination and culture of gastric lavage for *M. tuberculosis* had frequently been carried out. In table 1 the children are classified according to type of tuberculosis, age, and the bacteriologic findings. For the definition of the various groups the reader is referred to the original thesis (1).

In the present paper, the 1935 report is termed the "initial study." The surviving children, who have now reached adult age, have been re-examined. The aims of the investigation were to determine the prognosis of various types of tuberculosis in childhood with regard to the age at which the disease developed; the prognostic significance of bacteriologic findings in gastric washings at the initial examination; and the causes of death and the duration of survival after diagnosis.

For the sake of clarity the persons followed up have been placed in the categories they occupied in the initial study. This distribution, while perhaps not completely adequate by present-day standards, is still acceptable. In some tables in the present report certain groups have been combined. These consist of patients who originally showed active parenchymal lesions in a primary or secondary stage (*Group I A (1 a)*) and patients with active hilar adenitis with or without perihilitis (*Groups I A (2 a)* and *I A (2 b)*, respectively). These groups are collectively termed "primary tuberculosis." They are compared with cases of active pulmonary tuberculosis (*Group I A (1 b)*), designated "post-primary tuberculosis."

MATERIALS AND METHODS

Method of Follow-up Observations

The children were traced through population registers and the records of tuberculosis dispensaries. Of the original 434 children, records of 426 were available

[1] From Länssanatoriet, Uttran, Sweden.

[2] Sponsored by the Swedish National Association Against Tuberculosis.

[3] Presented before the Seventeenth Scandinavian Tuberculosis Meeting, Stockholm, September 10, 1954.

TABLE 1

DISTRIBUTION OF THE CHILDREN IN THE INITIAL STUDY ACCORDING TO TYPE OF TUBERCULOSIS, AGE, AND BACTERIOLOGIC FINDINGS

	0-3 Years		4-6 Years		7-10 Years		11-15 Years		Total		Grand Total	Per Cent Positive
	Gastric Washings											
	+	−	+	−	+	−	+	−	+	−		
I. Cases with positive roentgenographic pulmonary signs												
A. Active tuberculosis of lungs and hilar lymph nodes												
(1) With parenchymatous changes												
a. of primary and secondary type	39	7	23	9	22	9	12	7	96	32	128	75.0
b. of adult type	4	—	6	—	14	—	11	1	35	1	36	97.0
(2) With lymph node changes												
a. with perihilitis	18	12	16	12	19	17	4	3	57	44	101	56.0
b. without perihilitis	—	2	3	2	1	3	—	5	4	12	16	25.0
B. Inactive tuberculosis of lungs and hilar lymph nodes	—	4	—	27	1	56	—	34	1	121	122	0.8
C. Doubtful active cases	—	1	—	6	1	4	—	3	1	14	15	7.0
II. Cases with negative roentgenographic signs	—	3	—	7	—	4	2	—	2	14	16	13.0
	61	29	48	63	58	93	29	53	196	238	434	

for examination. The other 8 patients are now living abroad or are registered as missing. Forty-seven of the children are dead and the pulmonary status at death had been satisfactorily determined in all cases. Of the 379 survivors, all but 18 consented to re-examination by standard or mass roentgenography. This was undertaken at the hospital or tuberculosis dispensary nearest their homes. If such examination had closely preceded the follow-up survey, further films were considered unnecessary. The distribution in the original series of the 18 "non-participants" and the 8 "missing persons" is shown in table 2.

Nonparticipants and missing persons were few in number and were fairly evenly distributed in the various groups. In the following report, therefore, such persons will be disregarded.

TABLE 2

PARTICIPATION IN FOLLOW-UP

Showing Type of Tuberculosis and Bacteriologic Findings in Initial Study

Group (see table 1)	Follow-Up Study									
	Gastric Washings Initially Positive for Tubercle Bacilli					Gastric Washings Initially Negative for Tubercle Bacilli				
	Followed Up	Nonparticipants	Missing	Total	Per Cent Followed Up	Followed Up	Nonparticipants	Missing	Total	Per Cent Followed Up
I A (1*a*)	89	4	3	96	93	30	1	1	32	94
(1*b*)	29	4	2	35	83	1	—	—	1	100
(2*a*)	54	2	1	57	95	43	—	1	44	98
(2*b*)	3	1	—	4	75	11	1	—	12	92
I B	1	—	—	1	100	117	4	—	121	97
I C	1	—	—	1	100	13	1	—	14	93
II	2	—	—	2	100	14	—	—	14	100
	179	11	6	196	91	229	7	2	238	96

In the present study, 94 per cent of the children comprising the original series were roentgenographically re-examined.

Observation Period

The initial study was carried out from September, 1931, to March, 1934; and the follow-up study, in the three-year period 1950 to 1952. Thus the observation period in the surviving patients ranged from sixteen to twenty-two years. The great majority of the children, however, were first seen in 1933 and were re-examined in 1951, so that eighteen years was by far the most common observation period. For this reason, grouping of the series according to the duration of observation was considered unnecessary.

Roentgenographic Classification

The standard-size or miniature roentgenograms of 408 persons were examined. This total includes the 47 patients who died. In the roentgenographic assessment the following classification was employed:

No demonstrable lesions.

Calcification: Definite calcifications in the pulmonary parenchyma or hilar areas. Since the films were assessed by several examiners and the recording of small calcifications, particularly on miniature roentgenograms, is not always considered necessary, the number of persons in this category must be regarded as an understatement.

Inactive: Highly densified mottled and streaky parenchymal lesions of quiescent appearance. (Occasionally their inactivity was checked by culture of gastric washings.)

Active: Pulmonary lesions suggestive of active tuberculosis.

OBSERVATIONS

The results at the time of follow-up examination arranged according to the roentgenographic classification presented above are shown in table 3.

Healed or active lesions on follow-up examination: Signs of healed tuberculosis in the form of calcification or presumed fibrotic areas were demonstrated at

TABLE 3

ROENTGENOGRAPHIC CLASSIFICATION AT FOLLOW-UP

Group in Initial Study (see table 1)	Gastric Washings Initially Positive for Tubercle Bacilli						Gastric Washings Initially Negative for Tubercle Bacilli					
	Roentgenographic Status at Follow-Up			Dead		Total	Roentgenographic Status at Follow-Up			Dead		Total
	No Demonstrable Lesions	Calcification and Inactive	Active	Tuberculosis	Other Causes		No Demonstrable Lesions	Calcification and Inactive	Active	Tuberculosis	Other Causes	
I A (1 *a*)	33 37%	43 49%	3 3%	7 8%	3 3%	89 100%	17 57%	9 30%	— —	3 10%	1 3%	30 100%
(1 *b*)	1 3%	7 24%	2 7%	19 66%	— —	29 100%	— —	— —	1 100%	— —	— —	1 100%
(2 *a*)	22 41%	23 43%	3 6%	4 7%	2 4%	54 101%	24 56%	17 39%	2 5%	— —	— —	43 100%
(2 *b*)	1 33%	2 66%	— —	— —	— —	3 99%	4 36%	5 45%	1 9%	1 9%	— —	11 99%
I B	— —	1 100%	— —	— —	— —	1 100%	70 60%	36 31%	6 5%	4 3%	1 1%	117 100%
I C	1 100%	— —	— —	— —	— —	1 100%	9 69%	3 23%	— —	1 8%	— —	13 100%
II	1 50%	— —	— —	1 50%	— —	2 100%	10 71%	4 29%	— —	— —	— —	14 100%
	59 33%	76 43%	8 4%	31 17%	5 3%	179 100%	134 59%	74 33%	10 4%	9 3%	2 1%	229 100%

follow-up examination in 33 per cent of the persons whose gastric washings initially were negative for tubercle bacilli and in 43 per cent of those with initially positive bacteriologic findings. The difference is almost statistically significant, the probability of chance being less than 5 per cent. The sole inference permissible, however, is that, on roentgenograms taken sixteen to twenty-two years after a tuberculous infection in childhood, one in three of the persons with gastric washings initially negative for tubercle bacilli and two in five of those with initially positive gastric washings showed signs of healed tuberculosis.

The most interesting cases in the follow-up study are those in which the initial investigation showed active tuberculosis of the lungs or hilar lymph nodes (*Group I A*). This group is presented in table 4. In one column are shown all

TABLE 4

FOLLOW-UP ROENTGENOGRAPHIC FINDINGS IN PERSONS WITH ACTIVE TUBERCULOSIS AT THE INITIAL EXAMINATION

	Age at Initial Examination	Healed Lesions and No Demonstrable Lesions	Active Tuberculosis	Dead of Tuberculosis	Total
Primary tuberculosis (Group I A (*1a*), (*2a*), (*2b*))	0–3	63 93%	1 1%	4 6%	68 100%
	4–6	59 95%	1 2%	2 3%	62 100%
	7–10	56 85%	6 9%	4 6%	66 100%
	11–15	22 79%	1 4%	5 18%	28 101%
Total		200 89%	9 4%	15 7%	224 100%
Post-primary tuberculosis (Group I A (*1b*))	0–3	— —	— —	3 100%	3 100%
	4–6	1 20%	— —	4 80%	5 100%
	7–10	5 38%	2 15%	6 46%	13 99%
	11–15	2 22%	1 11%	6 67%	9 100%
Total		8 27%	3 10%	19 63%	30 100%
Grand total		208 82%	12 5%	34 13%	254 100%

persons in whom the follow-up roentgenograms showed inactive forms of tuberculosis (no demonstrable lesions, calcified and inactive lesions). The patients who died of unrelated causes are not included in table 4. In *Group I A* there were six such deaths. The respective causes were an accident thirteen years after tuberculosis was diagnosed, poliomyelitis after sixteen years, cardiac anomaly after three years, cerebral tumor after four years, and pneumococcal meningitis three years after the diagnosis of tuberculosis. At the time of death none of these 5 patients showed any signs of active tuberculosis. The sixth patient died of diphtheria ten months after admission to a tuberculosis sanatorium. Although the pulmonary disease was active, diphtheria was considered to have been the primary cause of death. A comparison was made between the children shown to have primary tuberculosis at the initial examination and those with post-primary lesions. As in previous reports, these categories are grouped according to age at diagnosis (table 4). Of the 254 persons included in table 4, 82 per cent showed no signs of active tuberculosis at the follow-up examination; 5 per cent had active lesions; the remaining 13 per cent had died of tuberculosis.

Mortality and morbidity of primary and of post-primary tuberculosis: There is a conspicuous difference in the mortality rates of the children with primary and post-primary tuberculosis. The figure for the former is 7 per cent and for the latter 63 per cent. This tallies well with the general experience that the prognosis of tuberculosis contracted in childhood is graver for post-primary than for primary forms (3, 4).

That the mortality in the primary tuberculosis group increased according to the age at which the disease was detected is also shown in table 4. In the children less than ten years of age at diagnosis, the mortality ranged from 6 to 3 per cent, while in the eleven- to fifteen-year-old group it was 18 per cent. This reflects the heightened tuberculosis risk during puberty.

In the children who originally showed post-primary tuberculosis, the death rate in all age groups was considerably higher than for primary tuberculosis. The relationship of fatality to age was to some extent reversed. From a 100 per cent case fatality rate in children less than three years old at the time of the diagnosis of post-primary tuberculosis, the death rate fell to 80 and 46 per cent, respectively, in the children aged four to six and seven to ten years at the time of diagnosis. However, in the eleven- to fifteen-year-old children, i.e., including the age of puberty, the figure rose to 67 per cent. Nevertheless, these groups were so small that the mortality rates cannot be considered to represent more than a trend.

Morbidity was also greater in the post-primary than in the primary group. Ten per cent of the former patients and 4 per cent of the latter showed active tuberculosis at the follow-up examination. In this case also, the numbers were too small to permit a statistically verifiable difference.

Ultimate prognostic significance of presence of tubercle bacilli in gastric washings during primary phase: The prognostic significance in primary tuberculosis of the presence of tubercle bacilli in gastric washings at the initial examination was studied. In table 5 it may be seen that, of the children who were discharging

TABLE 5

FOLLOW-UP ROENTGENOGRAPHIC FINDINGS IN PERSONS WITH PRIMARY TUBERCULOSIS AT THE INITIAL EXAMINATION

	Age at Initial Examination	Gastric Washings Initially Positive for Tubercle Bacilli				Gastric Washings Initially Negative for Tubercle Bacilli			
		Healed Lesions and No Demonstrable Lesions	Active Tuberculosis	Dead of Tuberculosis	Total	Healed Lesions and No Demonstrable Lesions	Active Tuberculosis	Dead of Tuberculosis	Total
Primary tuberculosis (Group I A (1*a*), (2*a*), (2*b*))	0–3	44 90%	1 2%	4 8%	49 100%	19 100%	— —	— —	19 100%
	4–6	37 95%	1 3%	1 3%	39 101%	22 96%	— —	1 4%	23 100%
	7–10	33 85%	3 8%	3 8%	39 101%	23 85%	3 11%	1 4%	27 100%
	11–15	10 71%	1 7%	3 21%	14 99%	12 86%	— —	2 14%	14 100%
Total		124 88%	6 4%	11 8%	141 100%	76 92%	3 4%	4 5%	83 101%

tubercle bacilli at the time of the initial study, 88 per cent showed no signs of active tuberculosis at the time of follow-up examination; whereas 4 per cent had active tuberculous lesions. The corresponding figures for the children with primary tuberculosis and no tubercle bacilli in the gastric washings in the initial study are 92 and 4 per cent. There is thus no clear difference in this respect between the groups; nor is the difference in mortality between the two groups (8 and 5 per cent, respectively) statistically verifiable.

From a prognostic aspect, therefore, the results of bacteriologic tests on gastric washings in the acute stage of primary tuberculosis are apparently without significance.

This view was also expressed by Wallgren (5). On the other hand, Poulsen and Andersen (6) found a higher death rate from tuberculosis in children who were discharging tubercle bacilli when first seen with primary tuberculosis than among those who were noninfectious at this time. The respective mortality rates in a total of 622 children less than ten years old were 20 and 5 per cent. The observation period was not stated. A similar experience was reported by Nissen Meyer (7). In 142 children less than twelve years old, who were tuberculin reactors and whose gastric washings were negative for tubercle bacilli, no deaths occurred; while, of 68 children in the same age group who were discharging tubercle bacilli, 4.6 per cent died of tuberculosis. The observation period, however, was only two years. Winkelmann (8) described only children with "open tuberculosis," i.e., all cases in which tubercle bacilli were demonstrated on microscopy of sputum or gastric washings. His series consisted of 154 hospitalized

children aged two to fourteen years and followed for three to thirteen years. The mortality rate in children who persistently discharged tubercle bacilli was 91 per cent. Of those discharged from the hospital in the noninfectious state, 29 per cent subsequently died of tuberculosis.

Active pulmonary tuberculosis: As shown in table 4, the follow-up survey revealed 12 cases of active pulmonary tuberculosis, 9 of which were originally recorded as primary and 3 as post-primary tuberculosis. Many of the patients have been ill for long periods and several have been treated with artificial pneumothorax or thoracoplasty. Detailed case histories are unnecessary for present purposes, but some idea of the patients' present condition may be gained from the following data.

	"Primary" Group	"Post-primary" Group	Total
Fit for work	4	1	5
Unfit for work, at home	3	1	4
Unfit for work, in hospital	2	1	3
Total	9	3	12

Thus, 42 per cent of the persons who still had active tuberculosis were able to work at the time of the follow-up investigation.

Deaths from tuberculosis: Thirty-four of the children who had active tuberculosis at the initial examination are dead. These have been classified into two groups. The first comprises deaths from tuberculosis of the lungs with nonmeningeal tuberculous complications, such as empyema, enteritis, and laryngitis, and is termed the "pulmonary tuberculosis" group. The second, the "meningitis" group, consists of patients who died of tuberculous meningitis with or without coexistent demonstrable miliary tuberculosis. The relationship between the cause of death and the bacteriologic findings is shown in table 6.

The proportion of children with gastric washings initially positive for tubercle bacilli was so similar in the pulmonary tuberculosis and meningitis groups that bacteriologic findings per se seemed to have no significance with respect to the chance of developing meningitis. Because of this the results of such tests are disregarded in the following analysis of the fatal cases.

TABLE 6

Initial Bacteriologic Findings in Fatal Tuberculosis

Gastric washings	Cause of Death		Total
	Pulmonary Tuberculosis	Tuberculous Meningitis	
Positive for tubercle bacilli	23 77%	7 23%	30 100%
Negative for tubercle bacilli	3 75%	1 25%	4 100%

TABLE 7

AGE AT DIAGNOSIS IN FATAL TUBERCULOSIS

Group	Age at Diagnosis	Total	Dead of Meningitis
Primary tuberculosis (Group I A (1*a*), (2*a*), (2*b*))	0–3	3	3 (100%)
	4–6	2	
	7–10	5	
	11–15	5	2 (40%)
Total		15	5 (33%)
Post-primary tuberculosis (Group I A (1*b*))	0–3	4	3 (75%)
	4–6	4	
	7–10	6	
	11–15	5	
Total		19	3 (16%)
Grand total		34	8 (24%)

TABLE 8

CAUSES OF DEATH

Cause of Death	Age at Diagnosis (years)				Total
	0–3	4–6	7–10	11–15	
Pulmonary tuberculosis	1	6	11	8	26
	4%	23%	42%	31%	100%
Tuberculous meningitis	6	—	—	2	8
	75%	—	—	25%	100%

In table 7 may be seen these cases grouped according to the type of disease at the outset (primary and post-primary tuberculosis), the age at which the disease commenced, and the cause of death. The commencement of the disease is regarded as the date on which pulmonary or hilar lesions were first detected. Previous manifestations from which the child had recovered, such as erythema nodosum or pleurisy, are not taken into account.

One-fourth of the deaths were due to tuberculous meningitis. In the children initially showing primary tuberculosis, the proportion was 33 per cent; and in those with post-primary lesions, only 16 per cent. The figures, however, are too small for statistical verification.

Fatal tuberculous meningitis was most common in the younger children. Of all the deaths from this cause, 75 per cent occurred in children less than three years old at the initial examination (table 8). Of the total deaths in this group, 86 per cent were due to meningitis (table 9).

The survival time for all 34 cases is diagrammatically presented in figure 1. This shows clearly the distribution of the causes of death in the primary and post-primary groups. As could be expected, no case of meningitis occurred in the

TABLE 9

AGE AT DIAGNOSIS IN FATAL TUBERCULOSIS

Age at Diagnosis	Cause of Death		Total
	Pulmonary Tuberculosis	Tuberculous Meningitis	
years			
0–3	1	6	7
	14%	86%	100%
4–6	6	—	6
	100%	—	100%
7–10	11	—	11
	100%	—	100%
11–15	8	2	10
	80%	20%	100%

first group more than seven years after the pulmonary disease was diagnosed, and none in the second group after more than ten years. It should be pointed out that in the period under review tuberculous meningitis was almost always fatal. None of the children in this series who developed meningitis survived. On this point, therefore, the study contributes to the somber background against which the advances made in recent years form such an encouraging contrast.

In 1933, Lundquist (9) reported a follow-up study of a series similar to that herein presented, consisting of children admitted to the same hospital as in the present study during the period 1910–1920. The total mortality in Lundquist's series was 24.3 per cent as compared with 13 per cent in the present study. Thus, the mortality from tuberculosis in children in this one institution fell by almost 50 per cent in the interval between the two reports.

In table 10 are presented the findings from other investigations undertaken about the same time as the initial study in this report and comprising children of similar ages and with similar types of disease. The results have been grouped according to the form of tuberculosis.

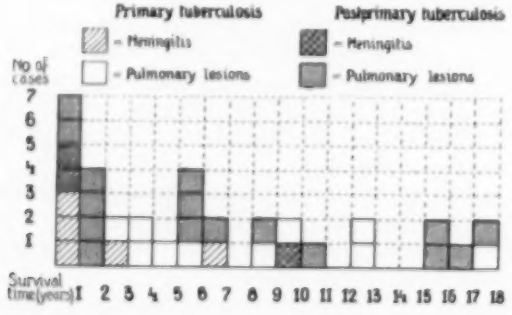

FIG. 1. Distribution of the 34 fatal cases according to survival time and cause of death

TABLE 10

FINDINGS FROM OTHER INVESTIGATIONS UNDERTAKEN AT SAME TIME AS INITIAL STUDY IN PRESENT REPORT

Author	Report Published	Number of Cases	Age	Period of Study	Observation Period	Mean Observation Period	Mortality
			years		*years*	*years*	*per cent*
All types of Intrathoracic Tuberculosis							
Lundquist (9)	1933	926	0–15	1910–1920	10–25		24.3
Beitle (10)	1938	496	0–7	1931–1935	1–8	4.3	5.5*
Holm (11)	1939	267	0–14		1–10		19.0
Levin	1955	254	0–15	1931–1934	16–22	18	13.0
Primary Intrathoracic Tuberculosis							
Nalbant (12)	1934	120	1–15	1927–1933	1–7		7.0
Wallgren (13)	1938	453	0–16				7.7
Denstad (14)	1942	120	0–6	1931–1941	1–11		6.0
Jaccottet and Nicod (15)	1946	347	0–14	1933–1943			12.1
Holmdal (16)	1950	657	0–15	1922–1937		15.4	4.9†
Bentley *et al.* (17)	1954	899	0–16	1942–1946		6	3.0
Lincoln (18)	1954	980	$^{3}/_{12}$–12	1930–1946			21.5
Levin	1955	224	0–15	1931–1934	16–22	18	7.0
Post-Primary Intrathoracic Tuberculosis							
Nalbant (12)	1934	120	1–15	1927–1933	1–7		49.0
Bentley *et al.* (17)	1954	116	0–16	1942–1946		6	48.0
Levin	1955	30	0–15	1931–1934	16–22	18	63.0
"Open" Pulmonary Tuberculosis							
Lundquist (9)	1933	84	0–15	1910–1920	10–25		86.9
Klare and Bohning (19)	1938	476	Children and youth	1926–1932	4–10		75.2
Simon (20)	1940	70	Pre-puberty			7	63.0
Winkelmann (8)	1950	154	2–14	1936–1946	3–13		67.0
Levin	1955	29	0–15	1931–1934	16–22	18	65.0

* Verified tuberculosis mortality—3.3 per cent

† Only patients with erythema nodosum

In table 10 it may be seen that the trend of the mortality figures was fairly constant, although the observation periods of the other reports were shorter than in the present investigation. Primary intrathoracic tuberculosis carried a relatively low death rate, ranging from 3 to 21.5 per cent, with a mean of approximately 7 per cent. For post-primary tuberculosis the mortality was considerably higher (49 to 63 per cent). "Open" tuberculosis showed the highest figures. All children who were discharging tubercle bacilli were included in the group designated "open" tuberculosis.

Thus, the results in the present study are in conformity with other reports in the literature. The existing discrepancies may to some extent be explained by variations in the composition of the different series, and by social and genetic factors.

The clinical material of the present study was derived from the pre-antimicrobial era. Only those persons who still showed active tuberculous disease at follow-up examination had received any antimicrobial drugs.

SUMMARY

Four hundred and thirty-four children with verified or suspected intrathoracic tuberculosis were followed up for periods ranging from sixteen to twenty-two years. Detailed roentgenographic and bacteriologic studies had been carried out in childhood. Follow-up roentgenograms were obtained in 94 per cent of the series.

Special study of the 254 children who initially showed active tuberculosis gave the following results:

In 82 per cent, the follow-up roentgenograms revealed no active tuberculous lesions. Five per cent had active disease and 13 per cent had died of tuberculosis.

The mortality rate of the persons who originally showed primary tuberculosis was strikingly lower than that of the children who originally showed post-primary lesions, viz., 7 and 63 per cent.

In the "primary" group the mortality rate increased with the age of the child at diagnosis. This trend was reversed in the "post-primary" group except in the children who contracted tuberculosis during puberty. Such children had proportionately high death rates in both groups.

Of the persons in whom the initial examination showed primary lesions and gastric washings positive for tubercle bacilli, 88 per cent were without active disease at follow-up examination and 4 per cent had active lesions. The corresponding figures for primary tuberculosis with negative gastric washings were 92 and 4 per cent. The results of bacteriologic tests on gastric washings during the acute phase of the disease would thus seem to have lacked prognostic significance.

Of the 12 persons with active tuberculosis at follow-up examination, 5 were fit for work. Analysis of the 34 fatal cases showed that death from tuberculous meningitis was more common in the children who initially showed primary lesions than in those with post-primary disease. In both groups most of the deaths from meningitis occurred in early childhood.

SUMARIO

Del Pronóstico de la Tuberculosis en la Niñez; Reseña de un Período de 18 Años de Observación

A 434 niños que tenían tuberculosis intratorácica comprobada o sospechada se les mantuvo en observación durante períodos que variaron de dieciséis a veintidós años. En la niñez se habían llevado a cabo minuciosos estudios radiográficos y bacteriológicos. En 94 por ciento de la serie, se obtuvieron radiografías durante el período subsecuente de observación.

El estudio especial de los 254 niños que revelaban al principio tuberculosis activa arrojó los siguientes resultados:

En 82 por ciento, las radiografías subsecuentes no revelaron lesiones activas. Cinco por ciento tenían enfermedad activa y 13 por ciento habían fallecido de tuberculosis.

El coeficiente de mortalidad en las personas que revelaron inicialmente tuberculosis primaria fué notablemente más bajo que el de los niños que tenían lesiones postprimarias, a saber, 7 y 63 por ciento, respectivamente.

En el grupo "primario," la mortalidad aumentó de acuerdo con la edad del niño al hacer el diagnóstico. Se invirtió esta tendencia en el grupo "postprimario," excepto en los niños que contrajeron la tuberculosis durante la pubertad. Esos niños tuvieron coeficientes proporcionalmente más altos de mortalidad en ambos grupos.

De las personas en quienes el examen inicial mostró lesiones primarias y lavados gástricos positivos para bacilos tuberculosos, 88 por ciento no mostraron enfermedad activa al hacerse el examen subsecuente y 4 por ciento tenían lesiones activas. Las cifras correspondientes para la tuberculosis primaria con lavados gástricos negativos fueron de 92 y 4 por ciento, respectivamente. Los resultados de las pruebas bacilares en los lavados gástricos durante la fase aguda de la dolencia parecen, pues, haber carecido de importancia diagnóstica.

De las 12 personas que tenían tuberculosis activa al hacerse el examen subsecuente, 5 estaban en aptitud de trabajar. El análisis de los 34 casos letales reveló que la muerte por meningitis tuberculosa era más frecuente en los niños que revelaron al principio lesiones primarias que en los que tenían afección postprimaria. En ambos grupos, la mayor parte de las muertes por meningitis tuvo lugar en la niñez temprana.

RESUME

Du Pronostic de la Tuberculose Infantile: Rapport sur 18 Années d'Observation

Quatre cent trente-quatre enfants atteints de tuberculose intrathoracique confirmée ou soupçonnée ont été suivis pendant des périodes variant entre seize et vingt-deux ans. Des études radiologiques et bactériologiques avaient été poursuivies pendant l'enfance. Des radiogrammes périodiques ont été obtenus dans 94 pour cent de cette série.

Une étude particulière de 254 enfants qui présentaient initialement une tuberculose active a donné les résultats suivants:

Dans 82 pour cent des cas, les radiogrammes périodiques n'ont révélé aucune lésion en activité. La maladie était active dans 5 pour cent des cas et 13 pour cent des malades ont succombé à la tuberculose.

Le taux de mortalité des sujets présentant initialement une primo-infection était nettement plus faible que celui des enfants présentant des lésions post-primaire, respectivement 7 et 63%.

Dans le groupe "primaire", le taux de mortalité s'accroissait avec l'âge de l'enfant au moment du diagnostic. Une tendance inverse était observée dans le groupe "post-primaire", sauf chez les enfants qui avaient contracté la tuberculose pendant la puberté. Chez ces enfants, le taux de mortalité était proportionnellement plus élevé dans les deux groupes.

Parmi les sujets chez lesquels l'examen initial montrait des lésions primaires avec prélèvements gastriques positifs pour le bacille de Koch, 88 pour cent ne présentaient pas de tuberculose en activité au cours des examens périodiques suivants et 4 pour cent avaient des lésions en activité. Les chiffres correspondants pour la primo-infection avec prélèvements gastriques négatifs étaient de 92 et 4 pour cent. Les résultats des tests bacillaires sur les liquides de lavage gastrique pendant la phase aiguë de l'affection paraissent ainsi dépourvus de signification pronostique.

Parmi 12 sujets présentant une tuberculose en activité au cours d'observations périodiques, 5 étaient en état de travailler. L'analyse de 34 cas ayant succombé montrait que la mort par méningite tuberculeuse était plus fréquente chez les enfants présentant initialement des lésions de primo-infection que chez ceux porteurs de lésions "post-primaires." Dans les deux groupes, la plupart des décès par méningite se sont produits dans la première enfance.

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Case Reports

TRANSITORY EXACERBATION OF FEVER AND ROENTGENOGRAPHIC FINDINGS DURING TREATMENT OF TUBERCULOSIS IN CHILDREN[1]

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In a previous report on the use of streptomycin in the treatment of tuberculosis in children (1), one of the present writers emphasized the disparity between the slowly subsiding roentgenographic findings, particularly those due to hilar adenitis, and the relatively rapid clinical improvement. In general, a definite improvement in the roentgenographic findings was not observed until the third month of therapy (1*a*).

Another interesting observation of that period was the aggravation of hilar adenitis during the course of miliary tuberculosis treated with streptomycin which occurred at a stage when the lung findings had started to subside. This was attributed to the congestion of the lung, which masked the outline of the adenitis in the beginning of the disease (1*b*).

The introduction of multiple-drug treatment with isoniazid-streptomycin (2–4) has considerably changed the treatment of tuberculosis in children, both in the relatively simple forms and in the more severe forms, such as meningitis.

During the treatment of the acute primary complex with isoniazid-containing regimens, a phenomenon occurred with sufficient frequency to make its occurrence as a coincidence most unlikely. The phenomenon consisted of the reappearance of fever for a five- to eight-day period during the second and third weeks after the beginning of treatment, and after the pretreatment fever had already subsided and the patient had improved clinically.

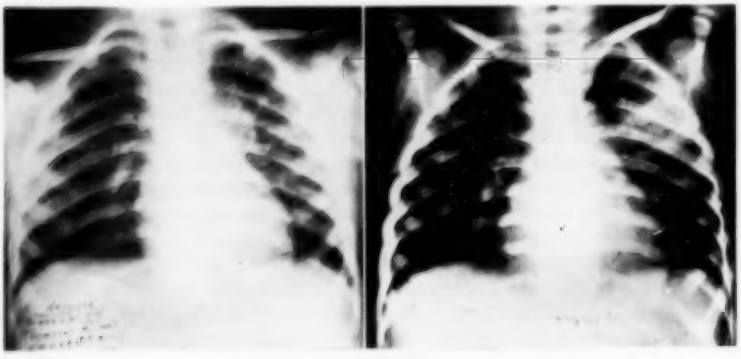
This return of fever under therapy has been observed in 22 of 43 patients treated in the clinic. The febrile exacerbation was not followed by an aggravation of the patient's condition, and symptoms suggesting an allergic reaction to the drugs were not observed. A careful clinical examination did not disclose any evidence of the occurrence of a non-tuberculous infection. In every case, however, there was an increase in the physical findings in the chest and an aggravation of the roentgenographic picture in the form of perifocal infiltrations or atelectasis. Consequently, it was believed justifiable to attribute the new elevation of temperature to the basic tuberculous disease. The duration of the fever usually ran parallel to the degree of exacerbation of the roentgenographic findings. The subsidence of these findings was slow, but a definite improvement was noted usually approximately a month later, at least in the patients studied for that length of time. In no case were any complications from other systems observed during this period of febrile exacerbation except for a mild meningismus in a few cases, but never a true meningitis.

The antimicrobial therapy was neither interrupted nor modified and the fever subsided by itself. It is worth mentioning that the severity of the febrile episode seemed to be related to the acuteness of the primary infection, i.e., it was more severe in primary infections with high fever and toxic symptoms.

[1] From the Pediatric Clinic of Athens University, Athens, Greece.

The following case reports are representative of this phenomenon as it was observed in the 22 cases as a whole.

Case 1 (B. B.). The patient was a 7-year-old female child who was admitted to the hospital on March 5, 1954. Her mother had active pulmonary tuberculosis. The child had a high fever of fifteen days' duration. On physical examination the child looked ill, with pallor and high fever. The tuberculin reaction was positive (Mantoux 1:10,000, 3-plus). The leukocyte count was 8,900 per cu. mm. and the differential count revealed a prevalence of lymphocytes. The erythrocyte sedimentation rate was 60 mm. (Westergren); the urine contained rare leukocytes, and no tubercle bacilli were found in the sputum.



Case 1

FIG. 1*A*. Roentgenogram of chest taken on admission to the hospital showing miliary tubercles uniformly distributed in both lungs from apex to base with prominent productive lesions.

FIG. 1*B*. Roentgenogram of chest taken approximately twenty-two days after beginning of treatment, showing no new lesions except some infiltration in left hilus.

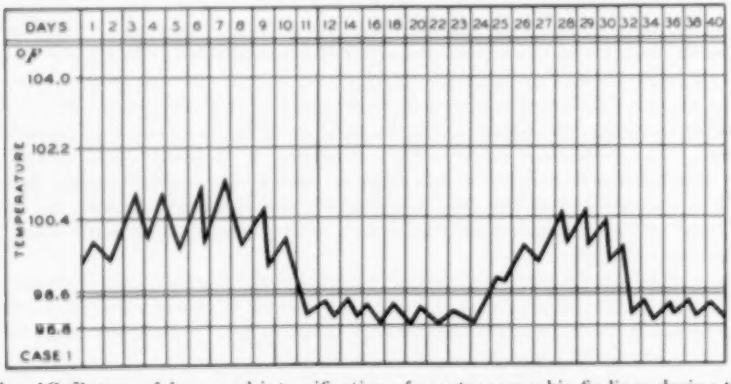


FIG. 1*C*. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of the chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

Roentgenographic examination on admission showed miliary tubercles uniformly distributed in both lungs, from apex to base, with prominent productive lesions. The roentgenographic diagnosis was hematogenous tuberculosis of the lungs with increased density in both hilar areas (figure 1*A*).

Therapy was started with streptomycin, 0.4 gm. twice daily, and isoniazid, 0.05 gm. four times daily (10 mg. per kg. of body weight). Ten days after the beginning of treatment, the temperature returned to normal and the patient's general condition was markedly improved. Twelve days later a new febrile wave (101.3° to 103.1° F.) was observed (figure 1*C*) while the patient's condition remained relatively good. Roentgenograms taken at that time revealed no other lesions except some infiltration of the left hilus (figure 1*B*).

The patient's temperature was elevated for approximately four or five days and then fell to within normal limits. Twenty days later and while the treatment was continued, another febrile wave appeared. The roentgenographic findings at this time were as follows: a marked enlargement of the density in the left hilar area combined with a perihilar reaction, but the parenchymal lesions were apparently regressing.

The fever lasted four days; the patient remained in the hospital for twenty days more, after which she was discharged in good condition.

Case 2 (C. No. 43 (855)). The patient was a 36-month-old female child who was admitted to the hospital on May 4, 1954, from the Foundling Hospital. She had a slight temperature, anorexia, and cough of ten days' duration. On admission the temperature ranged between 101.3° and 103.1° F. The tuberculin reaction was positive (Mantoux 1:10,000, 3-plus). The leukocyte count was 12,000 per cu. mm. with a prevalence of lymphocytes. The erythrocyte sedimentation rate was 25 mm. (Westergren). The sputum contained no tubercle bacilli and the urine was normal.

Roentgenographic examination on admission showed enlargement of the left hilus, with diffuse nodular infiltrations in the adjacent parahilar lung field. The superior mediastinum was displaced to the left (figure 2*A*).

Treatment was started which consisted of 2 × 0.2 gm. of streptomycin and 100 mg. of isoniazid (10 mg. per kg. of body weight).

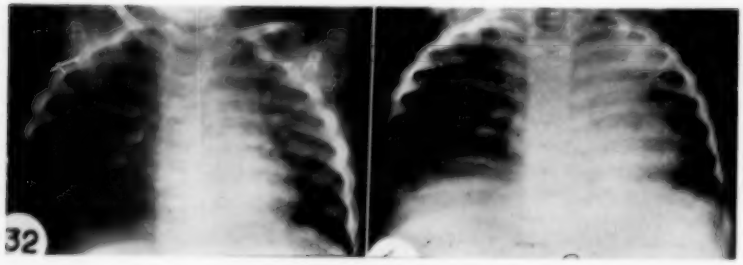
Eight days after the beginning of treatment, there was marked improvement and apyrexia. Ten days later a new febrile wave occurred (99.5° to 101.3° F.) which lasted four days, but was not accompanied by aggravation of the patient's condition. Roentgenograms taken at that time revealed typical atelectasis of the right upper lobe. The remaining lung fields showed no other findings (figure 2*B*). After five days the patient's temperature was normal (figure 2*C*). Approximately a month later she was discharged in good condition.

Case 3. The patient (S.) was a 10-month-old female infant who was admitted to the hospital on April 28, 1954, with a history of exposure to tuberculosis and a high temperature and cough of fifteen days' duration. Physical examination revealed nothing abnormal. The tuberculin reaction was positive (Mantoux 1:10,000, 2-plus). The leukocyte count was 11,000 per cu. mm.; the erythrocyte sedimentation rate was 45 mm. (Westergren). The sputum was positive for tubercle bacilli and the urine contained a few erythrocytes.

Roentgenographic examination on admission revealed a disseminated process in both lungs and increased density at the left hilar area, presumably due to enlarged tuberculous lymph nodes (figure 3*A*).

The patient was started on chemotherapy, consisting of streptomycin and isoniazid, the latter in a daily dose of 10 mg. per kg.

Four days after the beginning of treatment apyrexia with a good general condition was observed. Fifteen days later a new febrile wave of four to five days' duration occurred (figure 3*C*) while the patient's condition remained good. Roentgenograms taken at that time revealed an increase in the densities previously noted and atelectasis of the left upper lobe with soft nodular lesions conglomerated in both lungs (figure 3*B*). The patient was discharged forty-five days later in good condition.



Case 2

FIG. 2A. Roentgenogram of chest taken on admission to the hospital showing enlargement of the left hilus with diffuse nodular infiltrations in the adjacent parahilar lung field.

FIG. 2B. Roentgenogram of chest taken approximately eighteen days after beginning of treatment, showing typical atelectasis of the right upper lobe. The remaining lung fields showed no other findings.

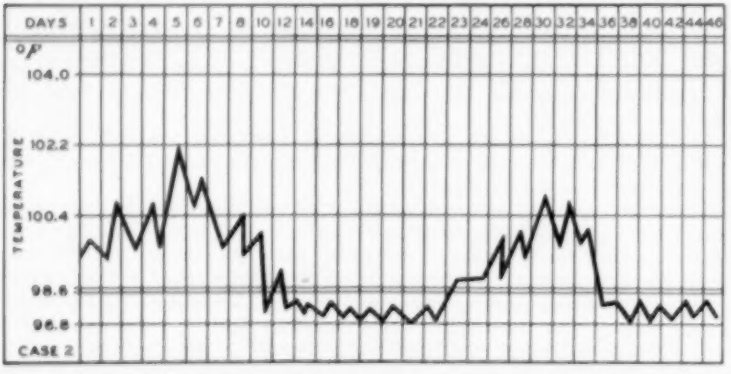
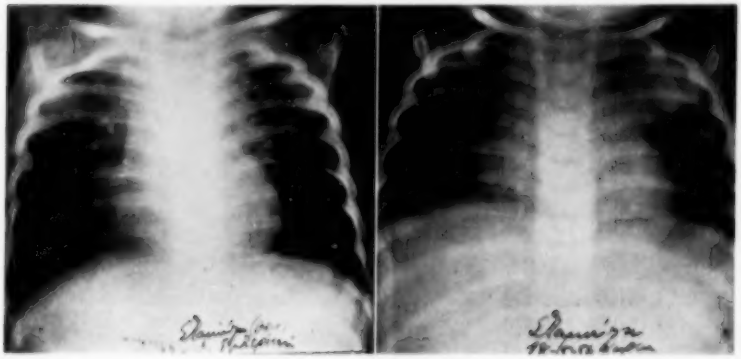


FIG. 2C. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of the chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

Case 4. The patient (K.D.) was a male child two and one-half years old who was admitted to the hospital on February 22, 1954. There was no familial history of tuberculosis or other known tuberculosis exposure. Following measles, the child had had a high temperature (102.2° to 104.0° F.) of eight days' duration. On admission to the hospital the child looked ill. Physical examination was unremarkable. The tuberculin reaction was positive (Mantoux 1:1,000, 3-plus). The leukocyte count was 12,000 per cu. mm. and the Diff count of 52 mm. revealed a prevalence of lymphocytes. The erythrocyte sedimentation rate was 84 mm. (Westergren). Sputum was positive for tubercle bacilli and the urine was normal.

The roentgenographic examination on admission showed increased density at the right hilus and widening of the right paratracheal lymph nodes, faint infiltration of the adjacent pulmonic parenchyma, and nodular-exudative processes in the left lung below (figure 4A).

Antimicrobial therapy with isoniazid-streptomycin was started. The same dosages were used as in the previous cases.



Case 3

FIG. 3A. Roentgenogram of chest taken on admission to the hospital, revealing a disseminated process in both lungs and increased density at left hilus, presumably due to enlarged tuberculous lymph nodes.

FIG. 3B. Roentgenogram of chest taken approximately nineteen days after beginning of treatment, showing an increase in densities previously noted and atelectasis of the left upper lobe with soft nodular lesions conglomerated in both lungs.

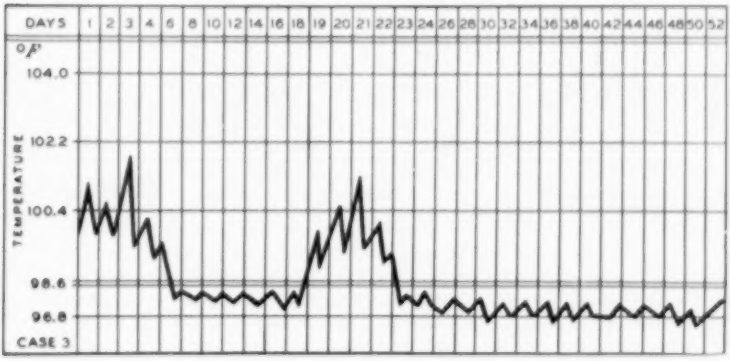
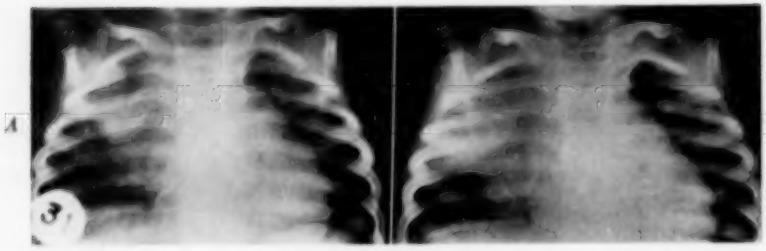


FIG. 3C. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

Ten days after admission improvement of the patient's condition and apyrexia were noted. Eleven days later a new febrile wave occurred (101.3° to 102.1° F.) while the patient's condition remained good (figure 4C). Roentgenograms taken at this time revealed increased markings in the right lung fields and infiltration of the right lobe, with nodular-exudative lesions at the adjacent base (figure 4B). Twenty days later the patient was discharged in good condition.



Case 4

FIG. 4*A*. Roentgenogram of chest taken on admission to the hospital showing increased density at right hilus and widening of right paratracheal lymph nodes, faint infiltration of the adjacent pulmonic parenchyma, and nodular-exudative processes in the left lung.

FIG. 4*B*. Roentgenogram of chest taken approximately twenty-one days after beginning of treatment, showing increased markings in the right lung fields and infiltration of the right lobe, with nodular-exudative lesions at the adjacent base.

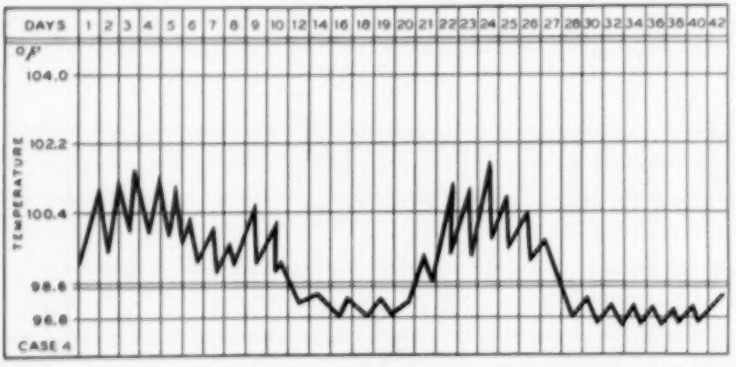


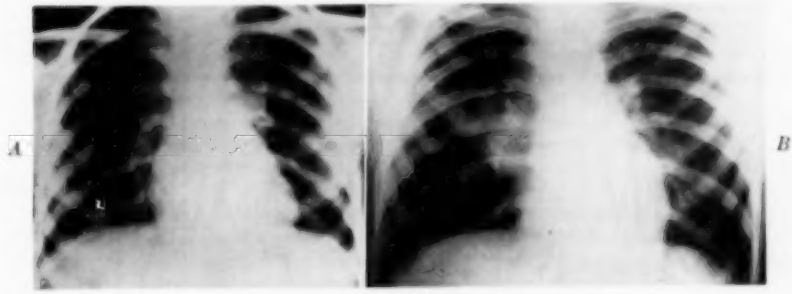
FIG. 4*C*. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

Case 5. The patient (B. L.) was a 6-year-old girl with no family history of tuberculosis. She had had a slight temperature of ten days' duration. On admission to the hospital the patient looked ill, was feverish (99.5° to 101.2° F.), and had anorexia. The tuberculin reaction was positive (Mantoux 1:10,000, 3-plus). The leukocyte count was 10,000 per cu. mm.; the erythrocyte sedimentation rate was 48 mm. (Westergren). The sputum was negative for tubercle bacilli.

Roentgenographic examination on admission to the hospital showed typical enlargement at the right hilus and infiltration of the right paratracheal lymph nodes with increased bronchovascular density in the right lung (figure 5*A*).

Treatment was started with isoniazid-streptomycin in the same dosage as was used in the other patients in this series.

Eight to ten days after the beginning of treatment, marked improvement and apyrexia were noted. Twelve days later a new febrile wave of four to five days' duration occurred



Case 5

FIG. 5A. Roentgenogram of chest taken on admission to the hospital showing typical enlargement at right hilus and infiltration of right paratracheal lymph nodes, with increased bronchovascular density in right lung.

FIG. 5B. Roentgenogram of chest taken approximately twenty days after beginning of treatment, showing increased infiltration of the regional parahilar parenchyma.

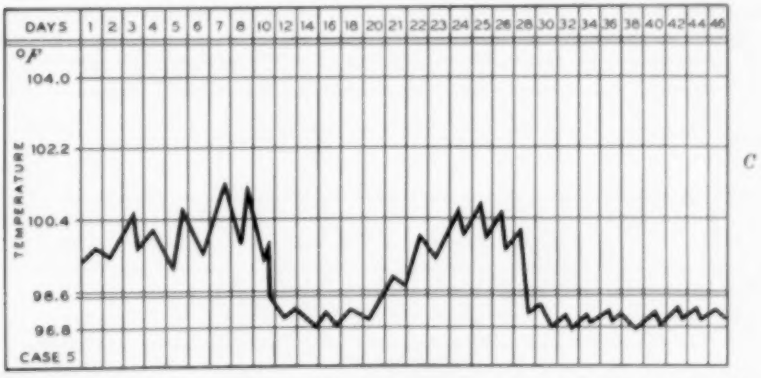
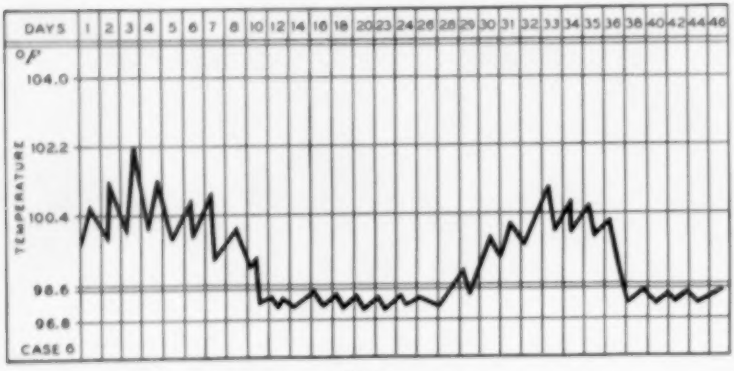


FIG. 5C. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

(figure 5C). No aggravation of the patient's condition was observed. Roentgenograms taken at that time revealed that, compared with the previous film, there was increased infiltration of the regional parahilar parenchyma (figure 5B).

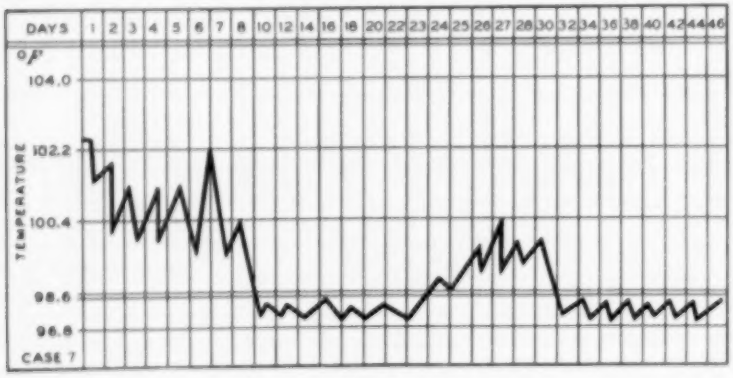
Case 6. The patient (P.P.) was a male child two and one-half years old who was admitted to the hospital on June 11, 1954. There was no family history of tuberculosis. The patient had had a high temperature of twenty days' duration. On admission he looked ill, weak, and had anorexia. Physical examination was otherwise normal. The tuberculin reaction was positive (Mantoux 1:10,000, 3-plus). The leukocyte count was 24,000 per cu. mm. The Diff count revealed a prevalence of polymorphonuclear neutrophils.

Roentgenographic examination on admission showed a typical increased density at the left hilus, presumably due to enlarged tuberculous lymph nodes, with perihilar infiltration.



Case 6

FIG. 6. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.



Case 7

FIG. 7. Return of fever and intensification of roentgenographic findings during third week of treatment of primary tuberculosis with isoniazid-streptomycin. Without alteration or interruption of chemotherapy, there was disappearance of the fever and satisfactory regression of the roentgenographic findings. The isoniazid daily dosage was 10 mg. per kg.

The patient was started on isoniazid-streptomycin therapy in the same dosages as were used in the other patients.

Ten days after the beginning of treatment, the temperature was normal and the patient was feeling well. Ten days later, while treatment was continued, a new febrile wave of six days' duration occurred while the patient's condition remained good (figure 6). Roentgenograms taken at that time revealed that, compared with the previous film, there was an increase in the densities and atelectasis of the left upper lobe (subclavian region).

The patient was discharged two months later in good condition.

Case 7. The patient (M. D.) was a 5-year-old boy with no family history of tuberculosis. He had had a high temperature of eight days' duration, anorexia, and weakness. On admission to the hospital the patient looked ill and his temperature was 101.3° to 102.2° F. The tuberculin reaction was positive (Mantoux 1:1,000, 3-plus). The leukocyte count was 10,000 per cu. mm. and the sputum was negative for tubercle bacilli.

Roentgenographic examination on admission showed an increased density at the right hilus with a faint parahilar infiltration.

Treatment consisted of the same isoniazid-streptomycin regimen as was used in the other patients.

Six days after the beginning of treatment, the patient's temperature became normal and his condition was good. Fifteen days later and while treatment was continued, the temperature was again elevated for four to five days (figure 7). The patient's satisfactory condition was not changed at this time.

Roentgenograms revealed marked aggravation in markings extending and infiltrating the perihilar field and the horizontal fissure. Five days later the temperature was again normal and the patient's general condition was good. He was discharged a month later, showing definite improvement.

COMMENT

The present investigation indicated that, during treatment with isoniazid-streptomycin of acute primary tuberculosis in children, a new elevation of temperature of approximately a week's duration frequently occurred between the second and third weeks. This febrile reaction was not usually accompanied by any worsening of the patient's general condition. The phenomenon has appeared so frequently in this clinic that the staff has almost come to anticipate it. The phenomenon was also observed during treatment with streptomycin alone but occurred less frequently and, hence, had not occasioned much attention.

Many of the patients with tuberculous meningitis in this clinic who were treated either with streptomycin alone or with isoniazid-streptomycin showed pyrexia associated with an aggravation of the cerebrospinal fluid findings which was attributed at that time to the treatment itself. A more detailed study of the cases in the present investigation revealed that the relapse of fever during the treatment of primary tuberculosis was always accompanied by an extension of process visible on the roentgenogram, either under the form of perifocal infiltrations or, in some cases, of atelectasis adjacent to adenitis.

The explanation of this phenomenon is obviously not easy. It is difficult to consider it as not bearing some relation to the form of treatment applied (6). In fact, it is believed that the exacerbation of the roentgenographic findings may be attributed to an intense exudative reaction which occurs under the influence of the treatment with isoniazid-streptomycin which might produce marked bacteriolysis and thus liberate tuberculin in large amounts. If such a process occurred, it might easily result in the development of perifocal infiltrations and atelectasis. It is known that the injection of tuberculin into a tuberculous host results in local focal reactions.

The very interesting work of Thiel (5) on the treatment of tuberculosis of the eye with amithiozone supports the above view. This writer distinguished two categories of patients: those who tolerated the drug without any reactions and those who exhibited inflammatory reactions during treatment. The reactions appeared four to six weeks after the administration of the drug or after an increase in dosage. In a few cases they appeared repeatedly in a rhythmical way. They consisted of typical focal reactions (*Typischer Herdreaktionen*) and rarely of new foci. Occasionally the reactions were not limited to

the eyes but extended to the pulmonary lesions. Thiel believes that, when the reactions were not exceptionally strong, they accelerated the healing of the tuberculous process. He interpreted the phenomenon as a liberation of toxic, tuberculin-like substances as a result of the action of the amithiozone. Thiel considered this phenomenon similar to observations made during the era when tuberculin was used in the treatment of tuberculosis. Finally, it is interesting to speculate on whether the use of cortisone might be justified during the transitory period of exacerbations noted during treatment with isoniazid-streptomycin, for cortisone has had extensive use in the treatment of tuberculous meningitis.

The start of treatment with isoniazid-streptomycin might conceivably produce a tuberculinization of the host and, by increasing the reactivity of the tuberculous foci, produce the development of perifocal infiltrations and atelectasis.

Addendum

Since the completion of this paper, 4 more typical cases of the return of fever during the third week of isoniazid streptomycin therapy have been observed in this clinic.

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A CASE OF AIR EMBOLUS DURING PNEUMOPERITONEUM[1]

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A sudden accident occurred during the instillation of air into a pneumoperitoneum. A description of this event forms the basis of the present report:

A male patient (J. V. P.), thirty-six years old, was admitted to the Sanatorio Durán in April, 1953. A diagnosis of pulmonary tuberculosis had been made in July, 1950, and the roentgenographic findings were interpreted as showing infiltrations with a tendency to caseation in the left upper lobe and a bronchogenic extension of the disease into the right upper lobe.

In July, 1951, a left intrapleural pneumothorax was initiated and was maintained during fourteen months. In April, 1953, a pneumoperitoneum was established but had to be abandoned after two months because of an abundant hemorrhage which implied the presence of adhesions. The patient was given isoniazid from June, 1952, until September, 1954, at which time sodium metansulfonate of isoniazid was substituted and administered until the present time. The patient also had been taking para-aminosalicylic acid (PAS) since November, 1953. In March, 1954, a left pleuropneumonectomy was performed because the pneumothorax had produced a total atelectasis of this lung. After the pleuropneumonectomy, some of the lesions in the right upper lobe reactivated and pneumoperitoneum had to be resumed on August 23, 1954. There was also a tuberculous inflammation of the right upper bronchus. Strong adhesions were presumed to be present because it could be observed on fluoroscopy that the liver was adherent to the diaphragm. Originally the punctures for the pneumoperitoneum were made in the left iliac fossa but, in view of the above-mentioned discomfort, the puncture site was changed to the right iliac fossa, almost at the point of MacBurney.

On October 18, the eighth puncture of the second series was being performed in the usual manner, without anesthesia, with a No. 20 needle with a guard. The patient was in the recumbent position, with his head a little lower than the rest of the body. The initial pressure was more than 7 cm. of water. Everything went well until, while insufflating 300 cc. of air, it was observed that the patient was grimacing. Asked what the matter was, he confirmed that he was in pain. He then became speechless and gradually lost consciousness. As soon as he had complained of pain, the insufflation was stopped and the pressure was checked and found to be greater than 9 cm. of water.

While the pressure was being determined and the needle was being withdrawn, the patient suddenly grew worse. He presented the following symptoms: loss of consciousness, tonic and clonic convulsions; progressive cyanosis; cyanotic and red spots which would appear and disappear; steadily increasing dyspnea; abundant foamy salivation; loosening of both sphincters (the patient defecated and urinated); bradycardia and hypotension (for a moment the pulse was not perceptible); and temporary blindness when consciousness returned.

As treatment has to be symptomatic, an attempt was made, first of all, to ensure an abundant supply of oxygen to the cerebral centers. In order to do this, the patient was placed in the Trendelenburg position, given an intramuscular injection of nikethamide (Coramine®), and 5 liters of oxygen were administered each minute. It was not necessary to use carbon dioxide or to treat the peripheric collapse because the patient recovered rapidly.

After a few moments the signs of peripheric collapse disappeared. At the same time the

[1] From the Sanatorio Durán, Cartago, Costa Rica.

patient began to recover consciousness. The cyanosis slowly subsided and the blood pressure rose gradually. The patient had begun to regain consciousness four minutes after the accident and was fully conscious within ten minutes. The blindness and a turbidity of vision took two more minutes to disappear. The dyspnea continued for half an hour. At this time the patient was given a cup of coffee, which he vomited. He was well except for a sensation of intense cold.

As soon as the patient had recuperated, he was taken to the X-ray room and a fluoroscopic examination was made. Nothing abnormal was found except that the intraperitoneal air chamber was very low (because of the above-mentioned adhesions). When he stood up, even though the arterial pressure was 80 systolic, 60 diastolic in mm. of mercury and the dyspnea had greatly diminished, he suffered a sudden hypotension that made him vomit violently. This ceased after he was placed in the Trendelenburg position. During the eight hours following the accident the patient complained of a slight headache, and he wanted nothing to eat that day. The tendon reflexes, motility of the extremities, consciousness, and vision were all normal.

COMMENT

The symptoms and the fact that the interior of the needle was full of blood when it was removed led to the conclusion that the syndrome had been produced by an air embolus. In order to prevent similar accidents during pneumoperitoneum, it would seem advisable to maintain the patient's head at a lower level than the rest of the body during and for a while after the puncture. The benign course of the above described case was probably partly due to the fact that the patient had been in this position. Abrupt movements should be avoided. No patient with strong intra-abdominal adhesions should be treated with pneumoperitoneum.

SUMMARY

An abrupt episode characterized by convulsive seizures, loss of consciousness, and temporary amblyopia occurred during the instillation of air into a pneumoperitoneum. It was concluded that air embolism had occurred although the mechanism by which this could happen remains obscure.

SUMARIO

Caso de Embolia Aérea Durante el Neumoperitoneo

Durante la insuflación de aire en un neumoperitoneo sobrevino bruscamente un episodio caracterizado por convulsiones, pérdida del conocimiento y ambliopía temporal. Dedújose que había ocurrido una embolia aérea, aunque permanece en la obscuridad el mecanismo que pudo motivar el percance.

RESUME

Un cas d'embolie gazeuse au cours d'un pneumopéritoine

Un incident aigu, caractérisé par des crises convulsives, perte de connaissance et amblyopie temporaire, est survenu pendant l'insufflation gazeuse d'un pneumopéritoine. L'auteur en conclut qu'il s'est produit une embolie gazeuse bien que le mécanisme l'ayant conditionnée demeure obscur.

Notes

RESISTANCE OF GUINEA PIGS TO INFECTION WITH SMALL NUMBERS OF VIRULENT TUBERCLE BACILLI MIXED WITH BCG

This report presents comparative tuberculosis mortality figures among groups of guinea pigs inoculated (*1*) with small numbers of virulent tubercle bacilli and (*2*) with equal numbers of virulent bacilli mixed with a suspension of a BCG strain. The purpose of the experiment was to determine whether the presence of a few virulent mutants in samples of BCG vaccine might escape detection by guinea pig passage. That such is the case with streptomycin-dependent tubercle bacilli has been demonstrated.[1] This strain, like the BCG strains, is incapable of producing progressive tuberculosis in the guinea pig and yet *in vitro* methods show that it contains a few (approximately one in 10^{-7}) non-dependent virulent cells.

The animals were inoculated with 10^{-6} and 10^{-7} dilutions of a culture of virulent tubercle bacilli, and plate counts later revealed that the number of bacilli inoculated was greater than was originally intended. Nevertheless, the animals were observed during a period of three and one-half years, at which time the survivors were sacrificed. The findings, in addition to revealing considerable individual variation in susceptibility to infection with virulent tubercle bacilli, indicate that the presence of a few virulent mutants in BCG vaccine would not necessarily be detected by guinea pig inoculation.

The strain of BCG used in this study was BCG 805, Series 2, Collection # 46338, obtained on Löwenstein medium from Dr. Konrad Birkhaug of the New York State Health Laboratories. The strain was carried in liquid Tween®-albumin; the dosage employed was 1 ml. of a 10^{-1} dilution of a ten-day-old culture. The culture was further diluted to 10^{-7} for plating to determine the number of viable units per ml., and it was thus established that the BCG dose contained approximately 20 million bacilli.

The virulent tubercle bacilli employed were the progeny of a single colony of stock strain H37Rv obtained from the tissues following guinea pig passage. A liquid Tween®-albumin culture of these bacilli was diluted to 10^{-6} and 10^{-7} in 0.1 per cent albumin in water. The number of viable units per ml. was determined by preparing a series of twenty oleic acid–agar pour plates[2] for each dilution, using 1 ml. of inoculum. Variation among the plate counts was greater with the 10^{-6} dilution because of the large number of colonies, but there was good agreement between the two dilutions; the average for the 10^{-6} plates was approximately 370 colonies while the average for the 10^{-7} platings was 39 colonies. It would have been better for the purpose of this experiment if a further dilution had been employed, but the findings are remarkable even with the relatively large 10^{-6} inocula.

The guinea pigs used were inbred albinos weighing between 700 and 800 gm. All failed to react to tuberculin (5 per cent Old Tuberculin (OT)) immediately preceding the study. They were divided into five groups of 20 animals each; one group received BCG alone (approximately 20 million viable cells); the second group received 1 ml. of the 10^{-6} dilution of H37Rv; the third group received 1 ml. of the 10^{-7} dilution of H37Rv; and the fourth and fifth groups received equivalent numbers of H37Rv 10^{-6} and 10^{-7}, respectively, plus the same number of BCG bacilli as the first group. Inoculations were made subcutaneously in the groin.

The intradermal tuberculin test was repeated at intervals during the observation period and the animals were inspected frequently for general appearance and were palpated for enlarged lymph nodes. A few animals were sacrificed for bacteriologic study. Necropsy

[1] Vanderlinde, R. J., and Yegian, D.: Am. Rev. Tuberc., 1951, *63*, 96.

[2] Yegian, D., and Budd, V.: Am. Rev. Tuberc., 1951, *64*, 81.

TABLE 1

DEATH OF GUINEA PIGS FROM GENERALIZED TUBERCULOSIS AS INFLUENCED BY SIMULTANEOUS INOCULATION OF BCG AND SMALL NUMBERS OF VIRULENT BACILLI

Time of Death	Infecting Dose				
	H37Rv 10^{-6}	BCG + H37Rv 10^{-6}	H37Rv 10^{-7}	BCG + H37Rv 10^{-7}	BCG
During first 12 months	8	1	3	1	0
12 to 24 months	3	5	4	5	0
24 to 42 months	5	7	6	2	0
Total for each group	16	13	13	8	0

was performed on all animals, and culture of the internal organs was carried out in those animals in which gross evidence of tuberculosis was not observed.

One month after inoculation, all of the animals reacted to the intradermal injection of 5 per cent OT and all had palpable inguinal lymph nodes on the side of inoculation.

The deaths from generalized tuberculosis in each group are listed in table 1. The largest number of deaths from tuberculosis, 16, occurred in the group of guinea pigs infected with H37Rv 10^{-6}; 8 of these occurred during the first year of the study. The group which received the same number of virulent bacilli plus BCG had only one death from tuberculosis during the first year, 5 during the second year, and 7 during the last year and a half; a total of 13 of 20 animals.

Fatal tuberculosis occurred in 13 animals in the group inoculated with H37Rv 10^{-7}; there were 3 deaths in the first year, 4 in the second year, and 6 in the third year. The H37Rv 10^{-7} plus BCG group had one death in the first year, 5 in the second, and 2 in the third year; a total of 8 deaths. There were no deaths from tuberculosis in the group which received BCG alone.

During the course of this study there were a few deaths from other causes, and occasionally animals were sacrificed for bacteriologic examination. In the H37Rv 10^{-6} group there were 2 deaths for which the cause is unknown. One occurred in the twenty-ninth month and smears of the internal organs were negative for acid-fast bacilli; cultures were not done. The other death occurred at thirty and one-half months and a few colonies of tubercle bacilli were recovered by culture of the tissues although no organisms had been seen on microscopy. In the H37Rv 10^{-6} plus BCG group there was one unexplained death at forty and one-half months. The only abnormal finding was a 2 by 3 mm. tuberculous abscess of the liver from which virulent tubercle bacilli were isolated.

In the group inoculated with H37Rv 10^{-7} there was one death from internal hemorrhage on the seventh day. Another death occurred in the thirty-ninth month; this animal showed no gross lesions and tubercle bacilli were not recovered by culture of the organs. Three animals in this group were sacrificed for study; 2 which were killed in the twenty-seventh and thirty-seventh months, respectively, showed no gross lesions, and cultures of the tissues were negative for tubercle bacilli; while the third animal killed in the fortieth month, showed one 2 by 3 mm. abscess from which tubercle bacilli were recovered.

Two animals died in the group which received H37Rv 10^{-7} plus BCG: one in the fourteenth month from unknown cause and the other in the twenty-first month from peritonitis due to intestinal perforation. Three animals were sacrificed in the eighteenth

month; 2 because of skin disease and one because of a jaw abscess. The internal organs of all 3 animals were grossly normal and cultures did not yield tubercle bacilli.

Nine of the animals which received BCG alone were sacrificed for study and one died of unknown cause in the eighteenth month. Two of the animals were killed in the eighth month and a few BCG colonies were recovered by culture of the internal organs. There were no gross lesions and cultures were negative for tubercle bacilli in 2 animals killed in the fourteenth month. Smears were negative and no gross evidence of tuberculosis was observed in 2 animals killed in the nineteenth month and in 3 animals killed in the thirty-second month which showed only a weakly-positive tuberculin reaction. Culture of the internal organs was not done.

At the end of forty-two months the surviving animals were killed. Two animals remained in the H37Rv 10^{-6} group; one of these had a 1-plus reaction to 5 per cent OT, the organs were grossly normal, and smears were negative for tubercle bacilli. The other survivor was obviously ill and did not react to tuberculin. Autopsy revealed a large retroperitoneal tumor (sarcoma) which weighed 130 gm. and measured 13 by 7 by 6 cm. The spleen, liver, and lungs were normal in appearance and smears of these did not contain acid-fast bacilli.

In the group of animals which received H37Rv 10^{-6} plus BCG, 6 survived the study and all were tuberculin-positive. Three of these showed no gross lesions and the organs were negative for tubercle bacilli by smear and culture. One animal showed grossly normal organs but a few colonies of tubercle bacilli were recovered on culture; one had a 3 by 5 mm. nodule on the liver which was positive on smear and culture; and the last had a small abscess in the groin from which tubercle bacilli were cultured.

There were 2 survivors in the H37Rv 10^{-7} group; both were tuberculin-positive, necropsy revealed no tuberculous lesions, and tubercle bacilli were not recovered by culture of the organs. In the H37Rv 10^{-7} plus BCG group, 7 animals survived; 6 were tuberculin-negative and one showed a weakly positive reaction. Gross lesions were not found in any of these animals nor were tubercle bacilli recovered by culture.

The 10 survivors in the BCG group were all negative to tuberculin; no gross lesions were observed and cultures were negative for acid-fast bacilli.

All of the survivors were in excellent nutrition and had gained considerable weight.

* * *

This study reveals differences in susceptibility to tuberculosis in groups of inbred guinea pigs inoculated with small numbers of virulent tubercle bacilli (approximately 370 and 38 cells, respectively), and with similar numbers of virulent bacilli mixed with a suspension of BCG. The observation period was maintained for three and one-half years, during which time the animals in the group inoculated with the larger number of virulent organisms succumbed to tuberculosis sooner and showed more fatalities than the group which received one-tenth as many bacilli. Although this is not an unexpected finding, it is of interest that in all groups inoculated with virulent tubercle bacilli some animals survived for three and one-half years and at necropsy showed either no gross lesions or a single, minute focus of infection. It was not possible to isolate tubercle bacilli by culture of the internal organs of some of these survivors. Those animals which were sacrificed or died of unknown causes during the latter part of this study also showed little or no evidence of tuberculous infection.

When BCG was inoculated simultaneously with virulent bacilli there were fewer deaths from tuberculosis and the survival time was longer. It is not known whether this difference is due to chance variation in individual susceptibility or to some factor intro-

duced by the simultaneous inoculation of BCG. It would seem, however, that the latter possibility must be considered.

No progressive tuberculosis was produced in any of the 20 animals which received BCG alone. One month after inoculation all of the animals showed marked hypersensitivity to tuberculin. The hypersensitivity to tuberculin was still present at the end of two years but had disappeared at three and one-half years in the 10 animals in this group which were kept throughout the study.

At the termination of the experiment all of the survivors reacted to tuberculin except those in the BCG group and 6 of the 7 survivors of the group which received H37Rv 10^{-7} plus BCG.

It is impossible to be certain that each of the animals in a group received precisely the same number of bacilli. Nevertheless, the uniformity of the plate counts in the higher dilution and the positive tuberculin reactions in the survivors which did not receive BCG indicate that these animals received an infecting dose. Therefore, the animals which received virulent tubercle bacilli plus BCG must have been similarly infected.

It is likely that, if one further tenfold dilution had been used in this study, i.e., a dosage of approximately 4 or 5 virulent tubercle bacilli, a greater number of animals would have escaped fatal infection. The number of virulent organisms in a back mutation would be expected to be small and it would seem, from the results of this study, that a few such mutants could well escape detection by guinea pig inoculation. It has recently been reported by Miller[1] that, in mice, it is possible to distinguish by histopathologic methods infections caused by virulent tubercle bacilli and infections due to BCG. It was possible by these methods to infect mice with as few as 270 virulent bacilli and to detect these when mixed with BCG in a ratio of 1 to 107,000. In this study the period of observation was only eight weeks and one wonders what the findings would have been if the survivors had been kept for a longer time. If the present guinea pig study had been terminated earlier, for example, at two months after inoculation, there would undoubtedly have been histologic and bacteriologic evidence of active infection in the animals which received virulent bacilli.

In summary: Two groups of healthy guinea pigs were inoculated with 10^{-6} and 10^{-7} dilutions of virulent tubercle bacilli, strain H37Rv, and two groups were inoculated with similar numbers of virulent bacilli mixed with a suspension of BCG. Another group of animals received only BCG. The guinea pigs were observed during a three and one-half-year period during which time none of the animals in the BCG group died from tuberculosis and those remaining at the termination of the study had lost skin hypersensitivity to tuberculin. There were survivors in all groups which received virulent tubercle bacilli. In the group which received the smaller number of virulent tubercle bacilli plus a suspension of BCG, 7 animals survived the three and one-half-year observation period and no evidence of tuberculous infection could be found. Six of these animals showed reversion of the tuberculin reaction and the seventh reacted only slightly to intradermal tuberculin.

It appears, therefore, that the presence of a few virulent mutants in a BCG strain would not be detected by guinea pig passage.

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[1] Miller, R., Jr.: Am. Rev. Tuberc., 1954, *70*, 1053.

BLOOD CONCENTRATION STUDIES WITH BUFFERED PARA-AMINOSALICYLIC ACID TABLETS

The ability of para-aminosalicylic acid (PAS) to delay the emergence of strains of tubercle bacilli resistant to other antituberculous drugs used concurrently with PAS makes it a valuable drug in the treatment of tuberculosis. This advantage is lost when the drug is discontinued or reduced in dosage because of drug intolerance of the patient. In many cases these unfavorable reactions take the form of gastrointestinal upsets such as nausea, vomiting, and diarrhea caused by drug irritation.

Buffered PAS tablets[1] are reported to be better tolerated than other currently used PAS preparations.[2] This tolerance is said to be due to the unique buffer[3] incorporated into each tablet, which reduces or prevents gastrointestinal upset.

The therapeutic efficacy of PAS tablets is not determined by tolerance alone, however, but by the attainment of adequate blood concentrations. Therefore, a study was undertaken to compare blood concentrations attained with buffered PAS tablets against those obtained with the more commonly used sodium PAS solution.

The method used for determining PAS blood concentrations is one developed in this laboratory[4] and gives results similar to those obtained by the procedure of Klyne and Newhouse.[5] It is based upon the formation of a yellow color produced by the addition of a solution of 3-methoxy-4-hydroxybenzaldehyde to a solution of PAS. The intensity of the color is proportional to the concentration of PAS in solution. The determination is performed upon protein-free blood plasma filtrates obtained by precipitating proteins with 20 per cent trichloracetic acid and by subsequent centrifugation and filtration. A portion of the filtrate is reacted with 3-methoxy-4-hydroxybenzaldehyde and the pH adjusted with sulfuric acid. The color intensity is then read spectrophotometrically and the reading compared with a previously constructed standard graph.

In order to determine blood concentrations following administration of buffered PAS tablets and of sodium PAS solution, three groups of either 5 or 6 patients each were chosen and, after discontinuation of medication for a thirty-six-hour period, each group was given the particular form and dosage of PAS to be determined. Two blood samples were taken from each patient at different hours and more than 150 determinations were performed.

Comparison of PAS blood concentrations which were reached following single doses of buffered PAS tablets and sodium PAS solution are shown in tables 1 and 2. In tables 3, 4, and 5 may be seen individual and average concentrations after multiple dosage with the two forms of PAS. The figures illustrate graphically, for rapid comparison, the averages of the individual results obtained with similar regimens of both buffered PAS tablets and sodium PAS solution.

* * *

There is general agreement among investigators that a concentration of 1.5 mg. of PAS in 100 ml. of plasma is bacteriostatic for tubercle bacilli, and that 2 mg. per 100

[1] A product of Panray Corporation, New York, New York.

[2] Bronx Veterans Administration Hospital: Quarterly Progress Report of the Veterans Administration-Army-Navy Study on the Chemotherapy of Tuberculosis, April, 1953, p. 14.

[3] The tablets consist of 0.5 gm. of PAS buffered with dihydroxy aluminum amino-acetate and calcium carbonate.

[4] Deeb, E. N., and Vitagliano, G. R.: J. Am. Pharm. A. (Scient. Ed.), 1954, *44*, 182.

[5] Klyne, W., and Newhouse, J. P.: Lancet, 1948, *2*, 611.

TABLE 1

PAS Blood Plasma Concentrations Following Single 4 Gm. Dose of Buffered PAS Tablets

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
5.7	6.4	1.7	2.3	2.6	0.6
5.7	1.3	5.6	3.7	4.4	0.9
2.5	6.1	3.7	2.5	4.0	1.7
1.1	3.5	6.1	4.0	1.4	0.6
3.2	4.0	2.7	4.0	1.7	3.6
1.6	1.7	5.1	3.5	1.5	1.9
Average of the Above Levels					
3.3	3.8	4.2	3.3	2.6	1.6

TABLE 2

PAS Blood Plasma Concentrations Following Single 5.5 Gm. Dose of Sodium PAS Solution*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.8	6.2	4.0	5.0	0.7	0.3
8.6	7.0	3.8	2.2	1.3	0.5
9.5	6.2	2.8	5.3	0.5	0.1
12.5	4.8	3.8	3.2	0.5	0.3
10.5	6.2	6.6	3.1	1.0	0.5
Average of Above Levels					
10.0	6.1	4.2	3.8	0.8	0.3

* Five and one-half gm. of sodium PAS are equivalent to 4 gm. of PAS.

TABLE 3

PAS Blood Plasma Concentrations Following Multiple Dosage with Buffered PAS Tablets

4 Gm. Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
8.3	6.8	7.2	5.1	4.6	4.0
9.5	10.2	8.4	5.1	4.4	2.9
12.8	8.0	7.6	3.5	5.1	4.6
9.5	7.2	6.6	3.7	4.0	2.5
7.7	9.8	4.6	3.4	1.9	0.9
Average of Above Levels					
9.6	8.4	6.9	4.2	4.0	3.0

* Samples taken after second dose of the day.

TABLE 4

PAS Blood Plasma Concentrations Following Multiple Dosage Therapy with Sodium PAS Solution

A Dose Equal to 4 Gm. PAS Was Given Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentrations in Mg. per 100 Ml.					
11.4	6.8	2.9	4.2	0.7	0.3
11.0	4.2	3.1	1.3	0.5	0.3
12.5	7.7	4.9	2.9	1.4	1.0
9.5	7.7	4.9	2.5	2.0	0.7
11.0	4.6	3.7	1.0	1.3	0.5
Average of Above Levels					
11.1	6.2	3.9	2.4	1.2	0.6

* Samples taken after second dose of the day.

TABLE 5

PAS Blood Plasma Concentrations Following Multiple Dosage with Buffered PAS Tablets

2 Gm. Three Times Daily*

1 hour	2 hours	3 hours	4 hours	6 hours	8 hours
Blood Concentration in Mg. per 100 Ml.					
2.2	3.0	4.0	1.4	4.0	2.5
3.3	2.4	3.7	4.6	0.7	0.5
2.9	4.4	4.4	1.7	1.7	1.3
4.5	3.7	2.9	4.9	1.4	0.9
3.6	3.1	3.3	3.7	2.0	1.4
Average of Above Levels					
3.3	3.3	3.7	3.3	2.0	1.3

* Samples taken after second dose of the day.

ml. or more is an adequate therapeutic concentration.[6] Determinations in this laboratory indicate that comparatively high blood concentrations are obtained in the first two hours after administration of sodium PAS solution. However, much higher concentrations are maintained for a longer period of time, after the first two hours, by administration of a single 4 gm. dose of buffered PAS tablets than with an equal dose of sodium PAS solution (tables 1 and 2). Therefore it appears that, if given in equal doses, blood concentrations obtained with buffered PAS tablets compare most favorably with blood concentrations found in patients who have received sodium PAS solution. This becomes more evident when, after multiple-dose therapy with equal doses of buffered PAS tablets and sodium PAS solution, the blood concentrations produced after the fourth hour by the administration of buffered PAS tablets are found to be approximately three times higher than those obtained with sodium PAS solution (tables 3 and 4).

[6] Nilson, H.: Tubercle, 1953, *34*, 100.

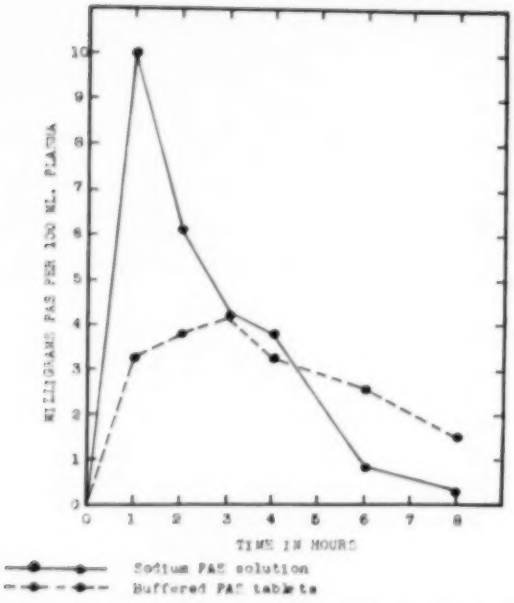

FIG. 1. Comparison of blood concentrations following single doses of sodium PAS solution and buffered PAS tablets. Each dose is equivalent to 4 gm. of para-aminosalicylic acid.

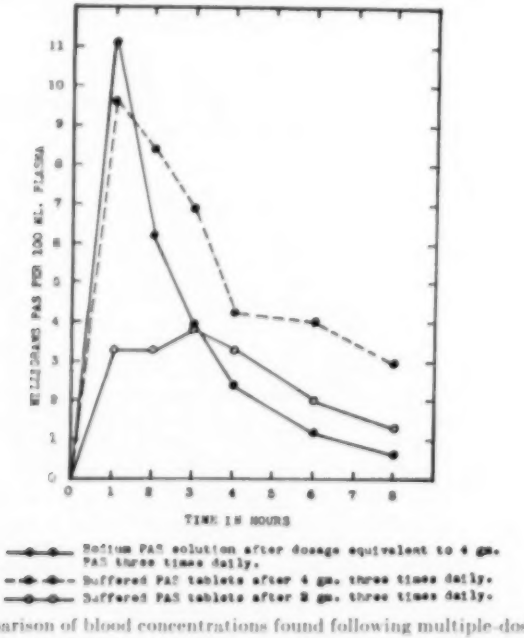
MILLIGRAMS PAS PER 100 ML. PLASMA
TIME IN HOURS
Sodium PAS solution after dosage equivalent to 4 gm. PAS three times daily.
Buffered PAS tablets after 4 gm. three times daily.
Buffered PAS tablets after 8 gm. three times daily.

FIG. 2. Comparison of blood concentrations found following multiple-dose therapy with different types and dosages of PAS. Therapy was interrupted to permit blood sampling at the time intervals indicated in figure 1.

TABLE 6

PAS Morning Blood Concentration Before Receiving Initial Dose of the Day

Patient	Blood Concentration in Mg. per 100 Ml.
1	0.3
2	0.5
3	0.7
4	0.4

Another advantage in the use of buffered PAS tablets, therefore, lies in the attainment and maintenance of higher blood concentrations after the final dose of the day as opposed to the concentrations produced by the more rapidly excreted sodium PAS. This fact is also expounded by Lehmann[7], who states: "The reason for not using the sodium salt (of PAS) is that it is very soluble in water, rapidly absorbed in the intestinal canal, and rapidly excreted in the kidneys."

Furthermore, the literature indicates that PAS blood concentrations determined at regular intervals after multiple oral dosage are usually higher than those taken at the same intervals after a single dose.[8] A study of tables 1 through 4 confirms this observation.

The data in table 1 indicate that an approximately therapeutic concentration exists six hours after a single 4 gm. dose of buffered PAS tablets; higher concentrations are obtained following multiple-dose therapy. The question therefore arose: Could not this therapeutic blood concentration be maintained a few hours more so that the patient could be adequately covered during the period from his late afternoon dose to his morning dose? Accordingly, 4 patients were chosen who were on multiple-dose therapy and were each given 4 gm. of buffered PAS tablets at 8 p.m. Before receiving this evening dose, patients *Nos. 1* and *2* had been on a dosage of 2 gm. three times daily. Patients *Nos. 3* and *4* were on a dosage of 4 gm. three times daily. Blood samples were taken at 9 a.m. the following morning before the patients received their morning dose of PAS. Results of blood concentration determinations are shown in table 6.

Further study was considered unwarranted due to low concentrations found in these morning samples. Apparently, a morning therapeutic concentration does not exist following a previous evening 4 gm. dose of buffered PAS tablets.

In summary: As blood concentrations with buffered PAS tablets compare most favorably with those obtained with sodium PAS solution, the buffered tablets may be advantageously administered to patients who are unable to tolerate other PAS preparations if their intolerance is due to gastrointestinal irritation.

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Edward N. Deeb[9]
Guy R. Vitagliano

December 13, 1954

[7] Lehmann, J.: Tr. Seventh Streptomycin Conference, Washington, D. C., 1949, pp. 293-300.

[8] Duncan, D. K., Carr, D. T., Pfuetze, K. H., and Power, M. H.: Dis. of Chest, 1951, *19*, 138.

[9] The writers are indebted to Dr. Stanton T. Allison, Chief, Tuberculosis Service, for his cooperation, generous professional assistance, and for his data on the clinical observation of the patients.

PARA-AMINOSALICYLIC ACID–RESIN COMPLEX: STUDIES IN ABSORPTION, SERUM ELECTROLYTES, AND TOLERANCE

The therapeutic value of para-aminosalicylic acid (PAS) in the treatment of tuberculosis, first demonstrated by Lehman[1] in 1944, has been amply confirmed by numerous investigators. The observation that the emergence of resistant strains of bacilli could be delayed by using PAS in combination with streptomycin made long-term antimicrobial therapy possible and led to its adoption in 1949 as a basic regimen in the treatment of tuberculosis. With the advent of isoniazid in 1952, the usefulness of PAS was again emphasized.

One of the great difficulties with PAS is its minor toxicity, manifested by nausea, vomiting, diarrhea, anorexia, and associated weight loss. This is true when the usual dose of 12 gm. daily is given, but the percentage of gastrointestinal symptoms rises precipitously when the total daily dose is increased beyond 15 gm. This capacity to produce gastrointestinal disorders has impaired the usefulness of the drug. Attempts to overcome this disadvantage have resulted in the preparation of PAS in various forms: coated granules, buffered tablets, effervescent tablets, and liquid preparations with masking agents. Recently PAS has been adsorbed on an anionic exchange resin (polyethylene polyamine methylene) to form an insoluble salt[2]. This preparation is a light, umber-colored powder which is tasteless, odorless, and stable. It readily mixes with foods without altering their palatability. In the gastrointestinal tract, chloride ions gradually replace the PAS in the resin and the liberated PAS is then absorbed in the usual manner. Since the gastrointestinal disturbance is proportional to the concentration of free PAS, it appeared likely that the PAS-resin complex would be an ideal preparation provided satisfactory serum concentrations of PAS were obtained and that no disturbance of serum electrolytes occurred when the drug was given for a long period of time.

For purposes of investigation, 17 male patients, varying in age from twenty-four to sixty, who had active tuberculosis and had had no previous chemotherapy were started on PAS-resin complex,[3] together with either streptomycin or isoniazid. Four of the patients had tuberculous pleural effusion, 7 had moderately advanced pulmonary tuberculosis, and 6 had far advanced pulmonary tuberculosis. Preliminary study consisted of chest roentgenograms, sputum examinations, complete blood counts, and determinations of blood urea nitrogen, prothrombin time, serum sodium and potassium, and body weight. Twelve grams of PAS (as the sodium salt) in solution were given for two days, and on the third day following the usual morning dose of 4 gm., serum concentrations of PAS were obtained at hourly intervals over a six-hour period. Total serum PAS was determined by using a modification of the Bratton-Marshall method.[4] PAS-resin complex was then given, 8 gm. three times a day, for the next six months. Serum sodium and potassium determinations, blood urea nitrogen, and prothrombin times were obtained at monthly intervals. PAS serum concentrations at random hours were obtained at two-week intervals during the experiment. At least once during this time each patient was given a single morning dose of 8 gm. of PAS-resin complex and its absorption was followed by hourly determinations of the serum PAS for the ensuing six hours. Two patients were dropped from the study. One left against medical advice after three months of therapy, while another developed sensitivity to both streptomycin and PAS, manifested by fever and dermatitis and confirmed by subsequent patch testing.

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[1] Lehman, J.: Dis. of Chest, 1949, *16*, 684.

[2] Marketed under the trade name of "Rezipas."

[3] Kindly supplied for this investigation through the courtesy of Dr. John T. Groel, Assistant Medical Director, The Squibb Institute for Medical Research, New Brunswick, New Jersey.

[4] Way, E. L.: J. Pharmacol. & Exper. Therap., 1948, *93*, 369.

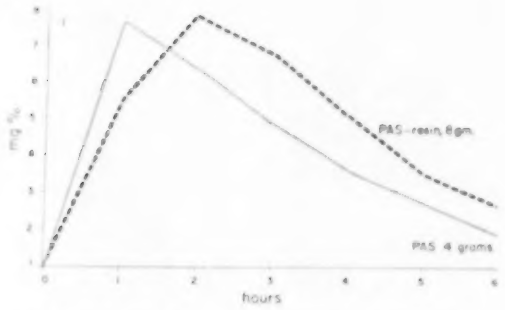


FIG. 1. Average absorption curves of 15 patients who had received PAS- resin complex

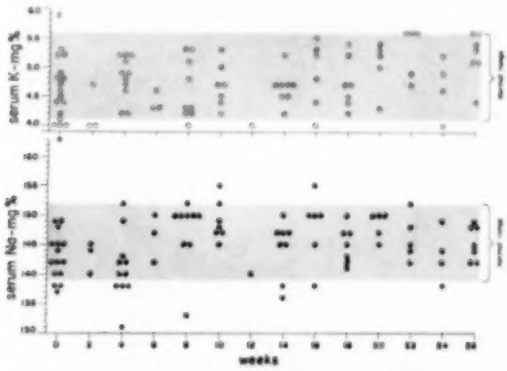


FIG. 2. Range of serum sodium and potassium during PAS-resin therapy

All patients tolerated and accepted the PAS-resin complex exceptionally well. There was not a single complaint of nausea, vomiting, or diarrhea although, when PAS in solution was given following the six-month study, 2 patients developed gastrointestinal symptoms requiring antacids, and in one of these PAS had to be discontinued.

The absorption of PAS from the resin combination as determined by measurements of the total PAS in the serum was equivalent to that of an equal amount of PAS in solution (figure 1). Concentrations as high as 11.4 mg. per 100 ml. were obtained after a single 8 gm. dose of the PAS-resin complex. The peak of the absorption curve occurred a little later and was sustained slightly longer when the PAS-resin complex was given.

There were minor variations in the serum potassium and sodium concentrations, but these were within the range of normal (figure 2). Initially one patient had a serum sodium determination of 163 mg. per 100 ml. which probably represents a laboratory error, since two weeks later the reading was 140 mg. per 100 ml., and subsequent determinations were all within the normal range. Likewise, patient *No. 7* had a serum sodium of 131 mg. per 100 ml. at four weeks which rose to 150 mg. per 100 ml. two weeks later and remained normal thereafter. No instance of hypokalemia was encountered. Prothrombin times, blood urea nitrogen, and blood counts all showed minor variations, but were well within normal limits.

The clinical, roentgenographic, and bacteriologic improvement of the tuberculosis was

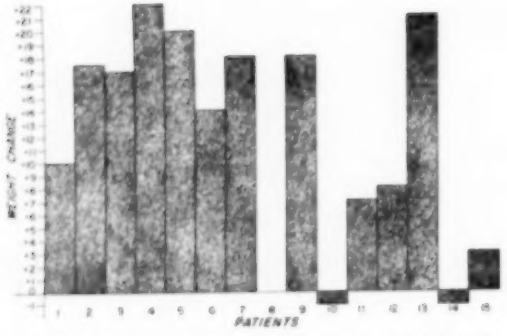
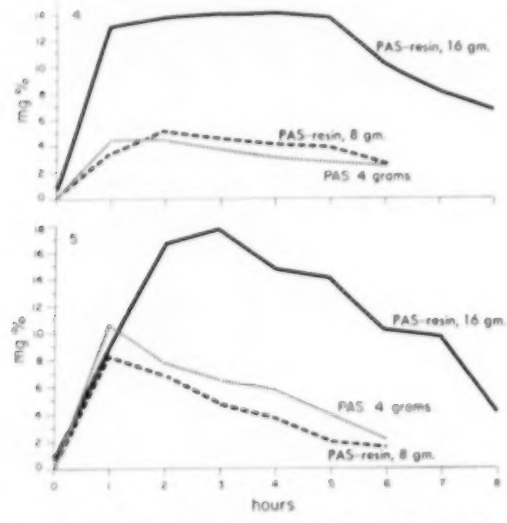


FIG. 3. Weight change at the end of six months during PAS resin therapy



FIGS. 4 and 5. Effect on serum levels of doubling dose of PAS-resin

equal to that which one would expect to see in patients under streptomycin-PAS therapy. The weight gain for the six months averaged 11.5 pounds, with 2 patients losing 1 pound and one remaining constant (figure 3). Patient *No. 10*, whose weight rose from 166 pounds at the start of treatment to 174 pounds at the end of the tenth week, had all of his teeth extracted at that time because of extensive pyorrhea. He was placed on a soft mechanical diet and his weight fell fairly rapidly to 165 pounds. Patient *No. 14* weighed 173 pounds at the start and 172 pounds at the completion of the experiment. Patient *No. 8* started with a weight of 132 pounds, rose to 136 pounds by the fourth week, and fell back to his starting weight of 132 pounds. Counterbalancing these losses were weight gains up to 22 pounds.

Two patients were given 48 gm. of the PAS-resin complex for a two-day period and, on the third day, following the morning dose of 12 gm., hourly PAS concentrations were determined. The serum concentration (figures 4 and 5) was approximately twice as high as that obtained with 24 gm. and, at the end of eight hours, 4 to 6 mg. per 100 ml. were still present in the serum. No gastrointestinal symptoms developed even with this large dose.

* * *

Para-aminosalicylic acid has long been recognized as a valuable drug in the treatment of tuberculosis. Unfortunately, from the time it was first introduced to the medical profession, its administration has been accompanied by gastrointestinal symptoms of sufficient frequency and severity to limit its usefulness. With the elimination of impurities, by preparing fresh solutions of the sodium salt as needed, preventing oxidation by shielding the solution from light, and keeping the bottle well stoppered and refrigerated, most patients can tolerate the usual 12 gm. daily dose. In spite of these changes, the incidence of gastrointestinal reactions still is significant and troublesome.

Gastrointestinal irritation from the drug is apparently related to the concentration of free PAS. When PAS is combined with a polyamine resin and ingested, the alkaline salts of the duodenum remove the PAS from the resin matrix, and slow diffusion of the drug follows. The major function of the resin is to maintain the concentration of free PAS below the irritation threshold of the gastrointestinal tract.[5] It does not interefere with the absorption of the drug and the usual dose apparently does not have any major effect on the duration of effective blood concentrations.

The administration of this preparation to 15 patients during a six-month period was characterized by excellent patient acceptance and complete absence of gastrointestinal symptoms. No disturbance of serum sodium or potassium occurred. Absorption levels were equivalent to those obtained when sodium PAS was given, and clinical, roentgenographic, and bacteriologic improvement was equal to that which one would expect to see in patients under conventional combined streptomyin-PAS therapy. Even when the equivalent of 27.5 gm. of sodium PAS was given over a three-day interval, no gastrointestinal irritation was experienced. It appears, therefore, that the PAS-resin preparation is one which eliminates the main disadvantage of PAS therapy.

In summary: A combination of para-aminosalicylic acid (PAS) with a polyamine resin is a therapeutically effective preparation. It did not cause any gastrointestinal disturbances in a group of 15 patients who received 24 gm. daily (equivalent to 12 gm. of PAS) for six months. Serum concentrations of PAS were equivalent to those obtained when 12 gm. of sodium PAS were given. No disturbance of serum electrolytes was found. In 2 patients, doses of 48 gm. of PAS-resin complex resulted in doubling the serum concentration of PAS without causing gastrointestinal disturbances although this was a short experiment.

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February 21, 1955

[5] Winters, J. C.: Personal communication to the author.

[6] Appreciation is expressed to Mrs. Anabel Phares for her assistance in assembling the data.

Correspondence

THE FATE OF THE IRREGULAR DISCHARGE TUBERCULOSIS PATIENT

To the Editor of the American Review of Tuberculosis and Pulmonary Diseases:

To the phthisiologist the problem of the irregular discharge patient has been a familiar one for years, and the longevity of the problem has not lessened its perplexity. One may still raise the question: Why does a patient with a disease which may well be fatal, if its treatment is neglected, leave the hospital and the treatment planned by an expert? Why does the patient leave against medical advice and what happens to him?

I do not propose to dwell in any detail on the probable causes of irregular discharges. There are several good articles in the literature dealing with this subject.[1-7] Suffice it to say that there are many factors influencing the patient to "cross the Rubicon" and leave the hospital against medical advice. Homesickness, economic problems, and factors arising outside of the hospital,[2] desire for the company of the opposite sex or alcohol, resentment of the doctor, the nurses, attendants, fellow patients, or the food in the hospital are, I feel sure, the chief factors. Occasionally the patient leaves because chest surgery has been suggested and the fear of surgery is so great as to panic him into leaving against medical advice.

It has been the impression of most of us that patients who leave a tuberculosis hospital against the advice of their doctors almost invariably get into trouble. Rates ranging from 80 to 90 per cent of unfavorable progression of disease have been quoted by many of us over the years, but do we know that they are true?

In order to obtain better than an impression of the fate of the "irregular" discharge patient, the author has sent questionnaires to all patients discharged during the years 1950 and 1951 from a 615-bed Veterans Administration hospital in New England for the treatment of tuberculous patients. It was decided that the questionnaire should be simple in outline, yet comprehensive enough for the doctor inspecting it to tell whether the patient who had filled it out was, at the time, an "inactive" or "active" case or whether the activity was "uncertain." In addition to sending a questionnaire to each patient, a request for information was sent to the Veterans Regional Office of the area in which each patient resided. This had to do with chest roentgenographic studies, with dates of chest films, sputum studies for tubercle bacilli (both microscopy and culture), and the clinic physician's appraisal of the patient's status. In addition to this, our outpatient department files were carefully checked for patients who might still be under observation by this hospital, and all the patients now in hospital were carefully checked.

There were 797 discharges[8] from the hospital during the years 1950 and 1951. Reports

[1] Simpson, R. M.: Am. Rev. Tubere., 1929, *20*, 29.

[2] Bobrowitz, I. D.: The Problem of Tuberculous Patients Leaving Against Advice, N. Y. Tuberculosis and Health Association, 1946.

[3] Quinn, D. E.: Bull. Nat. Tubere. A., 1947, *33*, 111.

[4] Quinn, D. E.: Bull. Nat. Tubere. A., 1948, *34*, 21.

[5] Veterans Administration: Irregular Discharge: The Problem of Hospitalization of the Tuberculous, V.A. Pamphlet 10-27, 1948.

[6] Tedesco, J. F.: Am. Rev. Tubere., 1953, *68*, 393.

[7] Lorenz, T. H.: Am. Rev. Tubere., 1955, *71*, 419.

[8] This did not include the patients who died in the hospital during those years nor pa-

on 577 of these 797 discharges are available, representing a total derived from four sources:

1. The patients themselves, on questionnaires returned by them.
2. The Veterans Administration regional offices holding patients' records who have data on post-discharge follow-up.
3. The patients being followed by our own outpatient department.
4. Patients who are now "inpatients" in this hospital. These are relapse patients who have been readmitted.

Of the 577 reports received, 276 concern patients who received a "regular" discharge and 301 concern patients who received an "irregular" discharge (A.M.A. or A.W.O.L.).

Number of Patients Reported

Regular Discharges

	Number	*Per Cent*
Total number: 276		
Dead	19	7.0
Inactive disease	180	65.2
Active	67	24.2
Activity uncertain	10	3.6

Irregular Discharges

	Number	*Per Cent*
Total number: 301		
Dead	50	16.6
Inactive disease	133	44.2
Active	102	33.9
Activity uncertain	16	5.3

In the two-year period, 797 patients were discharged from the Rutland Heights Massachusetts Veterans Administration Hospital, all of them having been treated for pulmonary tuberculosis. It has been possible to obtain a very satisfactory follow-up report on 577 of these patients. Of these 577, it was determined that 276 had received a "regular" discharge (maximal hospital benefit obtained, patients' case "inactive" or "arrested"); 301 patients had "irregular" discharges (left the hospital against medical advice before the case was brought to "arrest" or "inactive status").

Of the entire group of 577 reported upon, 69 (11.9 per cent) are dead. Of the group of 276 who received "regular" discharges, 7 per cent are dead and 93 per cent are living; 65.2 per cent have "inactive" disease and 24.2 per cent have "active" disease; 3.6 per cent have reports which are not conclusive and the activity of their disease is therefore "uncertain." Of the group of 301 who received "irregular" discharges, 16.6 per cent are dead and 83.4 per cent are alive; 44.2 per cent have "inactive" disease and 33.9 per cent have "active" disease; 5.3 per cent have inconclusive reports and the activity of their disease is classified as "uncertain."

It will be seen that more than twice as many patients who left the hospital against medical advice in 1950 and 1951 are dead as compared to those who were discharged as having had maximal hospital benefit (case "inactive" or at least "arrested").

In 1950 and 1951, long-term chemotherapy was coming into vogue but many patients were treated for only eight months, which today is generally regarded as too short a period for the treatment of pulmonary tuberculosis. Of the patients reported upon, a certain proportion received treatment at home in the form of chemotherapy; others were

tients who were admitted for observation and were discharged in less than a month as "inactive—no treatment required."

hospitalized in other hospitals and some of them received further courses of chemotherapy and some, in addition, received chest surgery.

Of the 301 "irregular" discharge patients, 143 (47 per cent) received further hospitalization; whereas, of the 276 patients who received "regular" discharges, only 38 (13.7 per cent) have had further hospitalization.

Undoubtedly the rather high percentage of "inactive" disease (44.2 per cent) in the patients who had received an "irregular" discharge from the hospital in 1950 and 1951 is due to the further hospitalization with further chemotherapy and, in some cases, chest surgery which they received subsequent to irregular discharge. It would appear that the patient who is discharged with a maximum hospital benefit (regular) discharge has a better chance of arresting his tuberculosis, and hence ultimately surviving, than has the patient who leaves the hospital against medical advice.

Stanton T. Allison

Tuberculosis Service
Veterans Administration Hospital
Rutland Heights, Massachusetts

April 22, 1955

Books

THE TUBERCLE BACILLUS IN THE PULMONARY LESION OF MAN. Histobacteriology and Its Bearing on the Therapy of Pulmonary Tuberculosis. By Georges Canetti (with a preface by René J. Dubos and Walsh McDermott). Springer Publishing Co., Inc., New York (also available from the National Tuberculosis Association), 1955, Price, $8.50.

To understand tuberculosis in man, it would seem that the chief concern of the pathologist would be to determine what responses of the host are associated with the multiplication of the bacilli in the tissues and which lesions spell the destruction of the microorganism. While there are experimental studies in animals which have contributed considerably to this problem, pathological monographs on the human disease are largely preoccupied with the histogenesis of the lesions, but almost exclusively from the standpoint of the host. Little attention has been given to the elucidation of the behavior of the parasite in man. Since the lesions are the expressions of the host-parasite relationships, it is clear that no understanding of their essential significance can be achieved in this manner.

The primary purpose of Dr. Canetti's monograph is a systematic study of the "histobacteriology" of pulmonary tuberculosis and its bearing on the therapy of the disease as practised in the days when rest and all its ramifications were its sole foundation and now, when chemotherapy has chiefly taken its place.

After reviewing the histogenesis of human pulmonary lesions, the essential contribution of the monograph is presented in the second chapter. It is obvious that rarely, and by chance, is it possible to study a human primary lesion within several weeks after the penetration of airborne bacilli into the alveoli, as has been done in animals. Nevertheless, what Dr. Canetti describes as the pre-exudative stage, in which tubercle bacilli (both isolated and in clumps) are found within intra-alveolar macrophages, may be the essential equivalent in man of this early phase of the infection in rabbits. Here the microorganism can be demonstrated to first multiply within these phagocytes. Soon caseation sets in. In its early phase, the caseous lesion swarms with bacilli. When the cells have completely disintegrated and solid amorphous caseum is formed the bacilli usually all but disappear and for the most part die. The author speaks of solid caseum as the "graveyard of the tubercle bacillus." The perifocal inflammation, particularly of the fibrinous alveolitic type, is an allergic phenomenon, prone to caseation, though poor in bacilli; for it is apparently penetrated by diffusion of bacillary proteins. It would be a great aid, Dr. Canetti remarks in this connection, if we would have histochemical methods to identify this bacillary protein and other constituents of tubercle bacilli. The epithelioid and giant cell tubercles, often seen at the edge of the caseous process, are usually poor in microorganisms.

Canetti finds this reviewer's studies on the significance of epithelioid cells and tubercle formation as resulting from the destruction of the bacilli "in remarkable agreement with those of man." Indeed, he feels that the two chief mechanisms of resistance in man are tubercle formation and caseation. Fibrosis is not the cause of healing but its result. Bacilli do not grow in fibrous tissue. They only do so during the process of softening. At this time there is "explosive" growth of the bacilli, as cavity forms and the fibrous tissue capsule disintegrates. In the presence of a "culture tube" of tubercle bacilli there is no immunity. The masses of bacilli from the softened caseum invade the bronchi and the disease spreads despite the existence of a high resistance.

Thus the dramatic story is told. Despite the special conditions that obtain in the human species, the essential pattern of the host-parasite relationships holds with but, as it were, variations on a theme for rabbits and guinea pigs as had been analyzed quanti-

tatively over the years. This is only to give a minute preview of this stimulating, eminently rational, and self-critical work.

Then follows a description of experimental studies on the fractions of tubercle bacilli and the role they play in the genesis of tuberculous lesions. The chapter on the relation of the lesion to immunity was particularly pleasing to an experimental pathologist, as Dr. Canetti has the gift of summarizing in a few bold strokes what is known and what is conjectural in this confused, much harrowed field. Of singular interest is the last chapter on the mode of action of rest and pulmonary collapse in the treatment of tuberculosis, the effect of antimicrobial drugs on the lesions and their contained bacilli, and particularly those in suspended animation in closed caseous foci. It would take away too much from the reader's pleasure and benefit if we should review this challenging chapter in detail. However, I cannot refrain from referring to one central observation of Canetti: the great increase in epithelioid and giant cell formation which is seen in resected lungs from patients under chemotherapy. This clearly points to the essential significance of the "metaplasia" in resistance to tuberculosis.

The book excels not only in the fund of its integrated data, the clarity of the exposition, its critical analysis but, with it all, Canetti has outlined many problems which are ripe for investigation. Their elucidation would be of significance not only in the field of tuberculosis but also in that of general biology.

MAX B. LURIE
Philadelphia, Pa.

THE LUNG. Clinical Physiology and Pulmonary Function Tests. By J. H. Comroe, Jr., R. E. Forster, II., A. B. DuBois, W. A. Briscoe, and Elizabeth Carlsen. Pp. 219, The Year Book Publishers, Inc., Chicago, Illinois, Price, $5.50

The purpose of this book, according to the preface, is "to explain in simple words and diagrams those aspects of pulmonary physiology that are important to clinical medicine." The authors' ideas on how to accomplish this purpose are concisely stated: "Pulmonary physiology can be explained in words, pictures, or equations. Most physicians shudder at equations; therefore words and pictures predominate and the occasional equation is accompanied by a verbal explanation and full apology. However, all important equations are presented in an Appendix for the enjoyment of those who have difficulty with words and pictures." What a delight to find a group of authors of the highest scientific competence who also know how to teach, and what a pleasant surprise to find a book in simple words and diagrams which does not do grave injustice to the subject!

This book presents a difficult subject simply, accurately, and amazingly completely. The early chapters deal with such relatively familiar items as lung volumes, pulmonary ventilation, and pulmonary circulation. Then ventilation per blood flow ratios are taken up, followed by diffusion across the pulmonary membrane, arterial oxygen, carbon dioxide and pH, and the mechanics of breathing. These later chapters go to the heart of some of the most difficult aspects of pulmonary physiology, and, particularly in the case of diffusion and mechanics of breathing, include the most recent advances in theory and practice. The reader is led gently from one step to another until in the course of a mere 141 pages he has been given every opportunity to grasp the basic principles of all this material. He can then, in the course of the next 29 pages, test his mettle on 10 clinical cases in which the history and pertinent physiologic data are given, followed by the authors' interpretation and conclusion. Finally, useful data, equations, calculations, and selected references are presented. Such comprehensive coverage in such understandable form requires art as well as science.

An urgent need for a book of this sort had arisen because of increasing interest in the subject on the part of clinicians in the absence of an authoritative book with clinical orientation. Now the doctors and medical students have no cause to complain. This book was written for them, and they may be surprised at what a fascinating subject is theirs for the reading, viewing, or deciphering.

Richard L. Riley
Baltimore, Maryland

Tuberculosis and Aspiration Liver Biopsy. Its Clinical Significance in Diagnosis and Therapy. By A. J. Ch. Haex and Cornelia Van Beek. Pp. 100, DeErven F. Bohn N.V., Haarlem, Netherlands, 1955.

This monograph reports for the first time in English the authors' extensive experience with aspiration liver biopsy in patients with tuberculosis.

Using a meticulous technique patterned after the one described by Iverson and Roholm, approximately 2,000 biopsies were performed without a single serious complication. More than 100 sections were made from each biopsy.

Of 189 cases of active tuberculosis (all forms), 176 (93 per cent) had histologic evidence of active tuberculosis in the liver biopsy specimen. Examination of liver biopsies from 150 "control" cases failed to reveal any evidence of tuberculosis. Bacteriologic confirmation of tuberculosis was obtained in only 71 (40 per cent) of the biopsy-positive cases. From these observations, the authors conclude that fresh hematogenous dissemination occurs in practically every case of active tuberculosis, irrespective of clinical form, and that liver biopsy is therefore a most valuable diagnostic and prognostic procedure to be used whenever, in the absence of contraindications, active tuberculosis is considered in a differential diagnosis.

Such sweeping conclusions require a much more critical review of the authors' investigations than is possible from this monograph. The plan and methods of study are not given in sufficient detail, diagnostic criteria for distinguishing sarcoidosis from tuberculosis are not described, and there are numerous discrepancies in the figures given, e.g., although the authors state that liver biopsy was performed in 189 cases of active tuberculosis, the numbers of such cases referred to in various sections of the monograph total well over 200; again, whereas in the text a statement is made that 14 of 20 cases of erythema nodosum had positive biopsies for tuberculosis, in Table II only 12 such positive biopsies are listed. Unfortunately, an unnecessarily large proportion of the monograph is taken up with repetitious and frequently irrelevant opinions about the treatment of tuberculosis and the merits of liver biopsy in patients suspected of having this disease.

In spite of these shortcomings, this monograph represents a real contribution by bringing attention to aspiration liver biopsy as a strikingly useful technique for studying the pathogenesis of tuberculosis as well as for assisting in its diagnosis. An appendix of 39 excellently reproduced photomicrographs adequately illustrate the five types of specific histologic changes described by the authors.

Aaron D. Chaves
New York, New York

Die Tuberkulosebekampfung in de Schweiz. La Lutte Contre la Tuberkulose en Suisse. Publication of the Swiss Tuberculosis Association Against Tuberculosis. Edited by H. Birkhauser. Pp. 374, S. Karger, Basel and New York, 1954.

This book was published on the occasion of the fiftieth anniversary of the Swiss League Against Tuberculosis. There are seven chapters written by various experts in the field.

They cover all aspects of the disease such as prevention, treatment, rehabilitation, and research.

The struggle against tuberculosis during the past fifty years is reviewed. It is shown how this fight was initiated by voluntary agencies in local communities, and was finally unified by special federal legislation.

The present status of antituberculosis measures compares favorably with that in other countries of western civilization, including the United States. There are some features within this program which seem to be of special interest.

Generally speaking, treatment in Switzerland differs little from the American routine. However, pneumothorax is still used in an appreciable number of cases, although less than in previous years. Resection is performed in only 20 per cent of the total surgery.

BCG is widely used and recommended, especially for children, medical personnel, and within the army.

Many of the medical insurances which cover a large part of the population have special provisions for tuberculosis. Sixty per cent of the population is thus insured against the disease.

The management and accomplishments of the fight against tuberculosis differ widely within the twenty-five cantons of the Swiss federation. This is due to the great variety of geographic and climatic conditions and to the cultural status of the three ethnologic groups forming the population of this country less in size than New York State.

One of these factors, namely the unique climate of the Alps, has added a special feature to the problem of tuberculosis in Switzerland. It has attracted consumptive patients from all over the world, who for many decades hoped to find cure in the dry climate of the mountains. Although climate is no longer considered a curing agent for tuberculosis, there are still many foreign patients in the numerous comfortable private hospitals and sanatoriums of Switzerland.

The book contains many detailed statistical tables. These statistics show the decline in mortality and shift in morbidity to the older age groups and the male sex, as observed in other countries.

This book is of interest to the student of tuberculosis.

Erna Lyon
Jamaica, New York

BOOKS RECEIVED

The Life of Bacteria. By Kenneth V. Thimann. Pp. 775, The Macmillan Company, New York, 1955, Price, $13.50.

A Textbook of Medicine. Ninth Edition. Edited by Russell L. Cecil and Robert F. Loeb. Pp. 1,786, W. B. Saunders Company, Philadelphia and London, 1955, Price, $15.00.

Differential Diagnosis. The Interpretation of Clinical Evidence. By A. McGehee Harvey and James Bordley, III. Pp. 665, W. B. Saunders Company, Philadelphia, Pennsylvania, 1955, Price, $11.00.

Heures Internationales dans la Lutte Contre la Tuberculose. By Étienne Bernard. Pp. 94, Masson et Cie, Paris, France, 1955, Price, 950 fr.

Röntgenanatomische Grundlagen der Lungenuntersuchung. By F. Kováts, Jr., and Z. Zsebők. Pp. 332, Akademiai Kiado, Budapest, Hungary, 1955.

Tumeurs Broncho-Pulmonaires. Exposés Anatomo-Cliniques. By A. Policard, *et al.* Pp. 146, with illustrations, Masson et Cie, Paris, France, 1955, Price, 1,000 fr.

Les Bacilles de Koch Incomplètement Evolués dans L'Infection Tuberculeuse. By L. Nègre and J. Bretey. Pp. 92, Masson et Cie, Paris, France, 1955, Price, 750 fr.

American Trudeau Society

Medical Section of the National Tuberculosis Association

The Award of the Trudeau Medal for 1954

The Trudeau Medal for 1954 was awarded to Dr. William H. Feldman at the annual meeting of the National Tuberculosis Association, held in Milwaukee, Wisconsin, May 22–27, 1955. The presentation was made by Dr. Edgar M. Medlar.

DR. MEDLAR: Much has been said about the importance of the patient-physician relationship. It is in this relationship that the art of medicine flourishes. In the practice of this art the physician learns well when to speak, what to say, and how to say it. As a pathologist it has been my lot to deal with specimens rather than patients and I have been unable to find any words of wisdom that pertain to the specimen-physician relationship.

I feel that I am in somewhat the same situation as a buck private who was being quizzed by his superior officer to determine his fitness for promotion. At one point this question was asked: "You have $36.61 in one pants pocket and $15.31 in another. What do you have?" Answer: "Sir, if there is that much money in these pants pockets, then I am wearing some other fellow's pants."

I am privileged to speak for your Committee in the presentation of the Trudeau Medal for most meritorious service in the field of tuberculosis. This year it seemed fitting to recognize the presence of a lusty adolescent chemotherapeutic progeny in our midst. In the growth and development of this youngster, some most admirable traits have become evident. However, certain unexpected and not so nice features also have developed—a common occurrence between birth and adolescence—and it is not yet certain what the character of the fully matured progeny may be. It is the wish of your Committee to do honor to one who assisted with the painful birth of this now robust youngster.

It has always been the hope of those who care for the sick to find a pill to cure an ill. As specific causes of illness become known there comes the urge to find specific pills for specific ills. This has long been the case with regard to tuberculosis. Although numerous chemical substances had been used from time to time in the treatment of tuberculous patients, it was not until 1938 that it began to appear that a survivor in this field was possible. One of the first conclusive demonstrations that experimentally produced tuberculosis could be favorably influenced by a chemotherapeutic agent was produced by the man whom we honor today.

This demonstration was not an accident. It is necessary for an investigator to be prepared for the day when an opportunity may arise and then to have the foresight, determination, and courage to pursue relentlessly the opportunity at hand. Therefore, it is pertinent to present a few incidents in the life of our subject that prepared him so well for later endeavors.

The citizens of the country town, population about 800, in which he grew to manhood were a rather unique group. They had a university club of more than fifty members. Half of his high school class went on to college at a time when the national average was 4 per cent. He played the cornet in the town band and, although he never became a virtuoso, he claims that he could blow loud and long. This ability helped to defray his expenses at college. He claims that the course in college studies which he pursued was chosen to avoid the subject of higher mathematics. I am unable to report any regret on this decision.

When he graduated, World War I was upon us and to his chagrin he found he could not serve since he was not a native-born citizen, having been imported at the age of two years. Before the matter of citizenship could be straightened out, the war was over. During the interim he was appointed as an instructor in pathology and bacteriology. He claims this occurred because no one else was available. Be that as it may, he remained as a member of the faculty, with advancement, over the ensuing ten years.

His first contribution to the literature on tuberculosis was a case report on tuberculosis of the tongue in 1927. The toughness of his mental fiber is well shown by the following quotation from this first article:

> Some mention that men in certain vocations, such as carpentry and shoe repairing, frequently carry in their mouths metal objects such as nails, and, of course, the likelihood of trauma that would permit the entrance of tubercle bacilli into the mucosa and underlying tissues is considerable. This explanation of the high incidence of tuberculosis of the tongue in the male is entirely inadequate when one considers that carpenters and shoemakers were conspicuous by their absence in the case histories reported.
>
> Some have placed, I think, undue emphasis upon the effect of pipe-smoking as a contributing factor in causing the tongue lesion. From the evidence presented in the reported cases, it is difficult to look upon pipe-smoking as playing any role whatever in the pathogenesis of tongue tuberculosis.
>
> The ages of the majority of the reported cases have been in the early forties. This, together with the fact that most of the tongue lesions have been secondary to pulmonary involvement, would suggest that the tongue is more prone to attack in the later stages of the disease and at a time when the resistance may be diminished.

The effect of this first venture into the land of the tubercle bacillus is clearly reflected in the publications from his pen through 1938. Of 105 publications, 44 dealt with some phase of the disease. These investigations included the study of the pathology and bacteriology in a wide range of naturally occurring acid-fast infections. They also included the morphologic changes found in experimentally produced disease in a considerable variety of unnatural animal hosts to different types of acid-fast bacilli. From this it is quite apparent that he was well prepared to undertake investigations with regard to the effect of chemotherapeutic agents upon experimentally produced tuberculosis as the various drugs became available.

His first paper on chemotherapy appeared in 1939. Since that date his name has appeared on 180 publications, of which 159 dealt with tuberculosis and, of these, 118 were concerned with the effects of chemotherapeutic agents.

That the value of team-work is greatly appreciated by this investigator is well shown by the fact that of 118 papers on chemotherapy he was a co-author of 110.

Although he has been an enthusiastic and tireless worker since the first gleam of success with chemotherapy was obtained, he retains the same tough mental fiber which was revealed in his first article on tuberculosis.

The following are a few brief quotations from his more recent writings:

> Since the earliest beginnings of drug therapy in tuberculosis it appears that whatever was new was considered proper in the treatment of the disease. This state of mind is, unfortunately, all too prevalent at the present time.

Again:

> In tuberculosis the problem is not that of simple septicemia or an acute inflammatory process but is instead that of an elaborate pathologic process con-

> sisting of bacteria of marked tenacity, relatively slow in their reproductive cycle, residing for the most part within the protection of physical elements that are frequently extensive and of long standing.

Again:

> In fact the disease in man is subject to such diverse manifestations as to represent not a single disease but many diseases. The existence of these differences in the pathogenesis induced by the same infective agent should be fully appreciated if one is to realize completely the magnitude of the problem that confronts the experimentalist in tuberculo-chemotherapy.

Again:

> Few indeed are the investigators who are experts in all of the allied fields of science that must be directed against this problem if progress of a reasonable tempo is to be attained. Group research in which the cooperative efforts of the biochemist, the pharmacologist, the bacteriologist, the biophysicist, the experimental pathologist and the clinician function as a harmonious team would, I am sure, contribute a greater volume of reliable basic information than is possible by any other approach.

Finally:

> Although modern chemotherapy of tuberculosis has contributed much in combating this disease, it is well to be reminded that the final conquest of tuberculosis is not yet in sight. Furthermore, there exist valid doubts whether the disease can ever be banished by the use of specific chemotherapeutic substances alone, even by drugs far more potent than any presently foreseeable.

So speaks the man on the printed page. What sort of fellow is he in daily life?

I am told his office is a place of orderly disorderliness, with notes stuck on the wall, sometimes with hypodermic needles. Directly in front of where he sits to ponder is the following note: "It matters not *who* is right but *what* is right."

He is a firm believer in the dignity and innate honesty of human beings. However, he will not compromise with ignorance or duplicity.

He is an expert photographer and has made all of the illustrations for his various publications. He has developed a penchant for portrait photography of men—to the exclusion of the fair sex. This to me is a puzzling phenomenon. This avocation has brought him a most unusual distinction. One of the subjects he photographed was a writer of detective stories and this author dedicated one of his later volumes to the photographer.

He is a gambler of sorts, as becomes all pioneers. Proof of this? He gambled a fifth of Old Crow on the outcome of one of his crucial experiments. I am unable to report why this particular vile brand was selected.

No man who ventures into the land of the unknown can avoid trying times. The manner in which such times of stress are met commonly reflect the credo of the man. The credo of the man to whom we now pay honor is clearly stated in this, his typical reaction to a trying situation: "For the past twelve years my professional activities have been concerned largely with the search for substances which might prove of value in treating the tuberculous patient. In the course of these investigations my associates and I have received for study numerous substances from many individuals and pharmaceutical concerns. . . . I have been afforded complete freedom to conduct my research in the best tradition of an academic community. This I consider to be the sine qua non of my scientific endeavors."

This son has lived true to an old saying of his adopted State: "Colorado is a place where men are men and tubs sit on their own bottoms."

Mr. President, on behalf of the Association and for most meritorious service in the field of tuberculosis, I will now present the Trudeau Medal to William H. Feldman, D.V.M., M.S., honorary D.Sc. and Professor of Comparative Pathology, Mayo Foundation, Graduate School of the University of Minnesota.

DR. FELDMAN: This occasion, and anticipation of it, are and will be for my family and myself, a continuing source of heartwarming satisfaction. I have not exchanged views with previous recipients of this award, but my emotional response probably has been similar to that of my predecessors. It is a response of humility and deep appreciation.

To be given the Trudeau Medal places the recipient on a pinnacle of personal and professional achievement in the field of tuberculosis. This is a sobering and momentous thought; to occupy a pinnacle confers not only felicity but responsibility. It requires of the occupant appreciation and understanding of what has been accomplished by others. For whatever we of today may have achieved, each of us is, in Tennyson's words, "the heir of all the ages," indebted to those who, with courage, imagination, hope and selflessness, made the first deposits in the account of our scientific legacy. So-called discoveries, with few exceptions, are the development to fruition of earlier, and sometimes of very old, concepts. Knowing this, humility rather than arrogance and self-aggrandizement provides priceless compensations which contribute abundantly to the joy of living and justify existence.

An obligation the award implies, which need not be emphasized to those of us who are teachers as well as investigators, concerns the graduate student. We must continue to instruct, guide, encourage, and stimulate those who aspire to share in the adventure of research—and thus we insure to ourselves the stimulus of their eager youth. This mutually rewarding relationship must be assiduously nurtured.

We who are recipients of this award must maintain our hope for a more nearly complete solution of the problems of tuberculosis. We must welcome new concepts with optimism and submit them to fair and critical appraisal. Whether a new proposal proves valuable or worthless, never should we view a succeeding proposal with cynicism—a pernicious, debilitating attitude and a killer of dreams. We must be ever ready and willing to serve where our experience and abilities can best be employed.

We must assume at least indirect responsibility for the conduct of proper public relations on the part of investigators. Unwittingly, investigators may assist in premature and inept announcements which appear to be newsworthy, but which are not in the best interests of the public. All of us have witnessed cruel disappointments following the sensational announcement of new and so-called miraculous substances that were hailed as the long-awaited means of salvation of the tuberculous patient.

When I was a boy in western Colorado, we relied for news of the world and of the nation on the weekly edition of the *New York World*. I recall vividly one issue in which considerable space was devoted to text and illustrations concerning Dr. Friedmann, of Friedmann vaccine fame. According to the story, he had arrived in New York from Europe, bringing with him quantities of his "lifesaving" vaccine for the treatment of tuberculosis. The reception given this news by victims of the disease was overwhelming. When, however, the results of the pseudoscientific fiasco were finally appraised, all that remained were the tragedies of cruel disillusion.

Advances in medicine are admittedly newsworthy but sensational announcements based on inadequate evidence, or those released prematurely, may be responsible for incalculable harm and are violations of a sacred trust. We are concerned here with human

frailty and the words of Sir William Osler are apropos: "With reason science never parts company, but with feeling, emotion, passion, what has she to do? They are not of her; they owe her no allegiance." If all this sounds pontifical, my excuse is that the subject has been of concern to me for a long time and I could not resist the opportunity provided by this occasion to express my conviction frankly.

During the past few weeks, friends have shown a surprising curiosity how I became interested in tuberculosis. That the question should be raised just at this time is perhaps a commentary on the ability or lack of ability to keep secret those things that are confidential. At all events, since this question may interest several in this audience, I am glad to furnish the answer.

I first became aware of the existence of tuberculosis when I was a youngster living in a mountainous area of western Colorado. For many years the salubrious climate of Colorado had been considered highly beneficial to those affected with what in those days was called "consumption." This idea became widely disseminated and, as a consequence, large numbers of tuberculous patients came from the East to "take the cure." The newcomers received a friendly welcome from the residents of the area and were not stigmatized because they had tuberculosis. Many lived—or at least slept—in tents since an abundance of fresh, dry, mountain air was considered the basic ingredient of the cure. I remember several worthy people in this category in our community. Some died. Others eventually recovered and either returned to their previous homes in the East or remained permanently in the area.

My mother looked on these unfortunate people with compassion. At times she supplied to a seriously ill patient a bed on her front porch. One victim of consumption died there. I also remember a neighbor, a rugged Scot, who had emigrated from Nova Scotia. He frequently mentioned the prevalence of tuberculosis there and cited instances in which most, if not all, members of certain families had succumbed to the "White Plague." All of this made a lasting impression on me, although I did not expect, at that time, to spend a good part of my life on investigation of tuberculosis.

Subsequently, my training in veterinary medicine acquainted me with the importance of tuberculosis in cattle and with the threat of the bovine type of infection to human beings. I also became aware of the ubiquitous character of tuberculous infections and learned that many species are susceptible to both the human and bovine types of tubercle bacilli.

During the time I was a member of the faculty of Colorado State College at Fort Collins, the leading surgeon of the community was Dr. W. A. Kickland. He recognized the importance to the surgical patient of the frozen tissue technique and he persuaded my chief, Dr. I. E. Newsom, a veterinary pathologist, to become skilled in the method. In due time, Dr. Newsom became one of the team when Dr. Kickland operated.

On one occasion when Dr. Newsom was out of the city, Dr. Kickland asked me to be present to make diagnosis by frozen section of a granulomatous lesion which he was going to remove from the tongue of a man thirty-six years of age. This patient had been affected with pulmonary tuberculosis for the previous fourteen years. Although I was by no means skilled in the procedure, I was able to make an acceptable stained section. After examination of the material, I was sure that it came from a tuberculous granuloma. Parenthetically, I would not be so sure now. When appropriately stained paraffin sections were prepared, I found acid-alcohol-fast bacillary forms within the substance of the lesion.

My interest aroused, I reviewed the literature and found that all who previously had studied the condition considered tuberculosis of the tongue to be of infrequent occurrence.

Accordingly, I prepared photographs to illustrate an article which the late Dr. Frank B. Mallory accepted for the May, 1927, number of the *American Journal of Pathology*. This was my first contribution on tuberculosis.

In 1927, when I joined the staff of the Mayo Foundation, facilities at the Institute of Experimental Medicine were available for the study of the comparative pathology of tuberculous infections. For nearly ten years, most of my time was occupied with investigation of naturally acquired, and experimentally induced, tuberculosis of animals. Consequently, when the opportunity arose to investigate the possibility of combating experimental tuberculous infections by specific therapeutic substances, the laboratory and especially trained technicians already were at hand.

In this undertaking I was fortunate in having as full partner my good friend, Dr. H. Corwin Hinshaw. Dr. Hinshaw had had experience in experimental methods and, in addition, as you well know, he was an astute student of clinical tuberculosis. Consequently, when we started the investigation of chemotherapy of tuberculosis, we had a considerable background of experimentation and firsthand knowledge of the disease. Most importantly, mutual understanding and cooperation made our work an exciting and pleasurable adventure.

Despite social and political upheavals, the past decade and a half have been a wonderful time to be alive. This is particularly true for those concerned with the attack on microbial diseases.

The history of tuberculosis and other mycobacterial infections, such as leprosy, is illustrative of the slow and, at times, discouraging progress of man's conquest of disease. Although knowledge of disease is greatly exceeded by ignorance of it, encouragement and reassurance accompany the frustrations and the disappointments. The periphery of the mysteries of disease recedes with each passing generation.

Some pronouncements to the contrary notwithstanding, science is still the dependable servant of mankind. The overly dramatized announcement recently accorded the results of the vaccine battle against poliomyelitis and the unfortunate confusion which has characterized the aftermath of this announcement do not in any way detract from the triumph of those who with faith and persistence have brought the problem of active immunization against poliomyelitis closer to solution. The encouraging results of the work of Dr. Salk and his associates, however, are only the most recent of a long list of notable advances against infectious diseases. One after another these diseases have fallen, and although you know them, let us for a moment gloat over the names of the vanquished: smallpox, whooping cough, diphtheria, malaria, typhoid fever, tetanus, bubonic plague, rickettsial diseases, and yellow fever. When Domagk observed the antibacterial capacity of Prontosil®, and Florey and Chain resurrected Fleming's penicillin from the obscurity of a medical library, the renaissance of modern chemotherapy had begun. The magnitude of these contributions to human welfare is incalculable.

The tuberculosis patient, who is more the immediate concern of us who are here, also has benefited significantly. Despite the failures of the past, the belief persisted that all microbial life, including the tubercle bacillus, was potentially vulnerable *in vivo* to the deterrent or destructive action of the proper chemical substance. In view of the long search for an antituberculosis substance of practical usefulness, the announcement in 1944 of the discovery of streptomycin by Schatz, Bugie, and Waksman was epochal in the history of medicine. This was the first relatively safe antimicrobial substance that was capable of exerting a markedly suppressive effect on tuberculous infections in the experimentally infected animal and when used clinically in human beings. These results provided considerable impetus to tuberculosis research throughout the world.

When the limitations of streptomycin became evident, several additional antituberculous substances were added to the rather limited armamentarium of the phthisiologist. While these newer drugs have not replaced streptomycin, their availability for use, either alone or in combination with streptomycin, has proved to be the basis of a definite therapeutic advance.

Whether or not the final conquest of tuberculosis ever can be accomplished by chemotherapy, surgery, and the best of medical regimens is unpredictable. Tuberculosis presents many enigmas and, before chemotherapy is completely successful, much must be learned about the host-parasite relationship. To penetrate the mysteries of this or any other complex biological problem, the investigator must have an agile imagination, a program, sound basic training, the capacity for arduous work, freedom to develop one's native resources, and financial support not for a year but for a period of years.

All research is expensive and this is especially true of investigations in the field of tuberculosis. Fortunately, in the past and for the present, the American public has made available, annually, large sums of money for research. These sums have been supplemented and exceeded by funds from the drug and pharmaceutical industry and from the Federal Government. How much of the yearly total from all sources is allocated for research in tuberculosis, I do not know. I do have information that the ten largest and most progressive pharmaceutical firms in America spend approximately $50,000,000 annually for research and that one of these ten concerns is currently spending for research in tuberculosis alone the rather impressive amount of $250,000 annually. Evidently, industry is not convinced that the problems of tuberculosis have been solved.

If the final victory over tuberculosis is to be achieved, the gains made must be zealously guarded; there must be no slackening of the attack, no contentment or complacency because of previous accomplishments. Rather, there is required a restless urge to get on with the task. With insight, optimism, and a winning way with Lady Luck, it is reasonable to expect that the mysteries of tuberculosis will be resolved.

Anyone who has engaged in laboratory research for any length of time soon becomes conscious of the debt of gratitude due his professional and nonprofessional associates. To acknowledge this obligation and express appreciation to those who through the years contributed so unselfishly to the advancement of my numerous investigational projects is indeed a genuine pleasure. Throughout my years in research I have been fortunate in having professional associates who were exceptionally capable. They had enthusiastic persistence, the insight and the capacity to think adventurously, and were not averse to work. Most importantly, they were able to function effectively as members of a team. Those to whom I am particularly indebted, and for whose collaboration I express warm appreciation, are my good friends, Dr. H. Corwin Hinshaw, whom I have already mentioned, Dr. Karl H. Pfuetze, and Dr. Alfred G. Karlson. Appreciation is also due the Mayo Foundation and the Mayo Clinic for providing generously, over many years, facilities for the conduct of our investigations. I want particularly to thank Dr. F. C. Mann, former Director of the Institute of Experimental Medicine, Mayo Foundation, for his understanding, his wise counsel, and his disposition to allow us complete freedom in the conduct of our investigations. Lastly, a tribute is due our loyal and dependable technicians, without whose assistance our work could not have been accomplished.

The Award of the Will Ross Medal for 1954

The Will Ross Medal for 1954 was awarded to Frederick D. Hopkins at the annual meeting of the National Tuberculosis Association, held in Milwaukee, Wisconsin, May 22–27, 1955. The presentation was made by Dr. Alton S. Pope.

DR. POPE: The Will Ross Medal is in a broad sense a recognition of the multiple causation of tuberculosis. While recognition of the tubercle bacillus and our increasing knowledge of its life history hold their essential place in tuberculosis control, we have increasingly come to recognize the importance of the environmental factors which affect both the organism and its human host. In fact, the role of such factors was accepted by our founders by the inclusion of education of the public as one of the major objectives of the new Association. So while physicians and scientists have advanced our medical knowledge of the disease and its causation, an equally devoted group has been building up a nation-wide organization for the dissemination of that information and its effective application.

It was in commemoration of a great leader in that field that the Will Ross Medal was established. It is for that type of outstanding, devoted service in the conquest of tuberculosis that the award is made.

Today we are apt to take for granted the well-organized, smoothly functioning voluntary health association which makes it so easy to muster public support for demonstrated health needs. In 1915, The National Association for the Study and Prevention of Tuberculosis was still far from its present mature, effective state. The objectives had been clearly stated, inspired leaders had blazed the way, but much of the detail of organization and the coordination of the work of existing state and local agencies was yet to be worked out.

It may seem repetitious to remind you of such accomplishments as the development of our field organization, the replacement of family relief with educational programs, the coordination of the work of the Association with that of the official health agencies, and participation in the development of the International Union Against Tuberculosis, both as a contributor and as a recipient. These are all milestones in the growth of the National Tuberculosis Association. In all of these developments and many others our recipient has been to a unique extent the unseen catalyst, seldom appearing but contributing silently and effectively to the increasing momentum of the tuberculosis control movement.

If it appears that his accomplishments have been swallowed up in those of the Association, it is because his career has been inseparable from the objectives of that organization in which he has played such a vital role. His personality is so well known to you all that any personal tribute would seem superfluous. His tact and his modesty are reflected in the countless friendships which bind us to him as a man. For his accomplishments, above and beyond the call of duty, the National Tuberculosis Association presents to Frederick Dan Hopkins the Will Ross Medal for 1955.

MR. HOPKINS: Since Dr. Pope wrote me a few weeks ago to advise me of the action of the Committee, my mind has been filled with thoughts of the past and with growing recognition of my inability to express any suitable thanks for this high honor.

For forty years I have had one of the greatest satisfactions—participation in the voluntary tuberculosis movement in the United States. I wish to express again, as I have many times, the debt that I owe Philip P. Jacobs for inducing me to join the staff of the National Tuberculosis Association in 1915.

Almost everything that has been undertaken in the National office has been a joint activity and therefore anything for which I may have been given credit has been aided

or influenced by many others. In my early work in the field I can testify to the same preponderance of joint effort. So many people made such valiant efforts to keep me from making mistakes. Then, too, I had the privilege of working under the leadership of four outstanding managing directors, Dr. Charles J. Hatfield, Dr. Linsly R. Williams, Dr. Kendall Emerson, and Dr. James E. Perkins, whose advice, forbearance, and at times gentle restraint, made possible accomplishments that otherwise would have been impossible.

The executive office has always had such fine working relationships with the Board of Directors that, as I look back on events, I have the feeling that no national voluntary agency in the health or welfare field has been so fortunate in its policy-making body.

It is most pleasing to me that the name and likeness of Will Ross are on the medal. When Will Ross left us I was among those who urged that his name should be preserved in some way so that it might be known to those who came later. It is a special honor to receive this award in Milwaukee, the home of Will Ross. He was a distinguished citizen of this city and in the business world was favorably known and respected nationally. He devoted time and effort over a long period of years to the voluntary tuberculosis movement on a local, state, and national basis. His influence on the work of the NTA is shown in the reports of many committees, the Board of Directors, the Executive Committee and the program of the Association during his presidency. He was powerful in discussion and debate; his words were few but always well chosen and persuasive, and his timing was perfect. Far more than this and perhaps of equal importance were his glowing personality, his vast knowledge of the disease based on his personal struggle with it, and his many letters and conversations that affected the course of events.

The Will Ross Medal, and the Memory Books that you gave me in 1951, will always be my most treasured possessions. Once again, I thank you.

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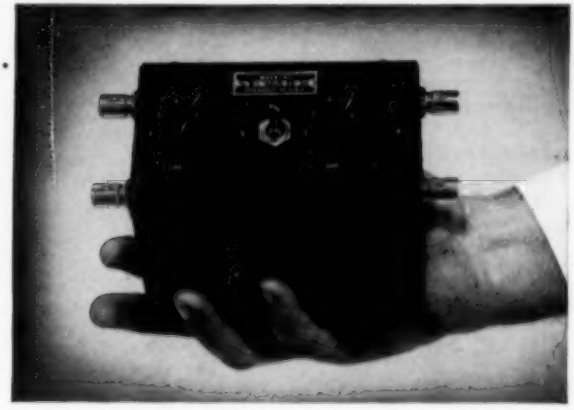

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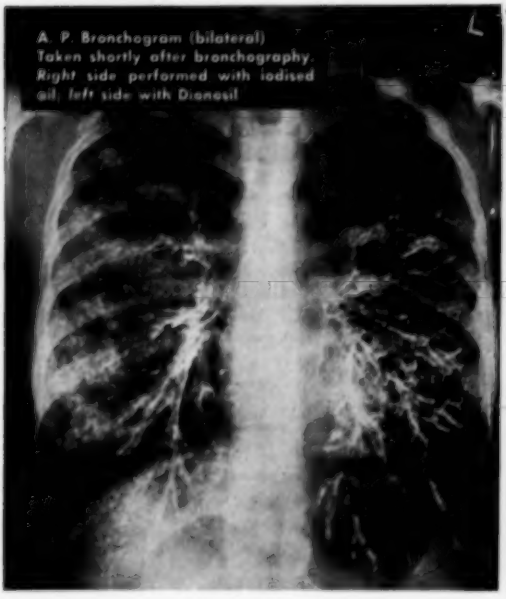

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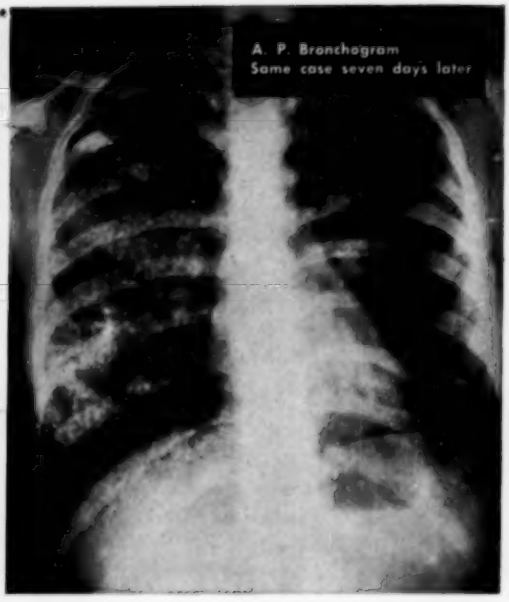
Taken shortly after bronchography.
Right side performed with iodised oil; *left* side with Dionosil



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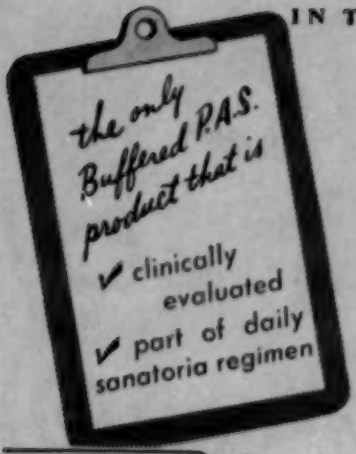

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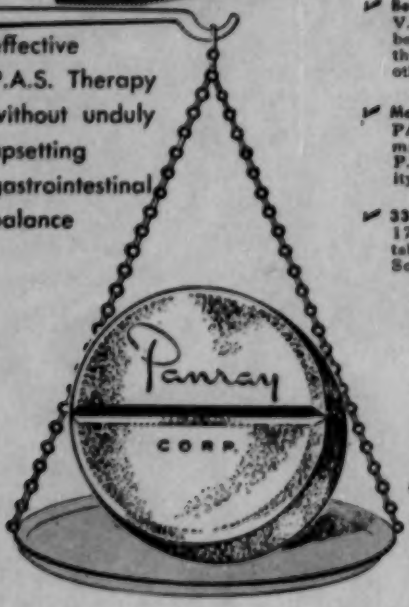

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References:

(1) *V.A. Quarterly Prog. Report, April '53 Bronx V.A. Hosp. N. Y.*

(2) *V.A. Quarterly Prog. Report, Oct. '54 Rutland Heights V.A. Hosp. Mass.*

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